FORMULATION AND EVALUATION OF CHRONOMODULATED PRESS-COATED PULSATILE THERAPEUTIC SYSTEM FOR CARVEDILOL

Dissertation work submitted to
THE TAMILNADU Dr. M.G.R.MEDICAL UNIVERSITY, CHENNAI.
In partial fulfillment of the requirements for the award of degree of

MASTER OF PHARMACY
IN
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BY

REG. NO: 26105106

Under the guidance of

Dr. V. Ganesan M. Pharm., PhD.,
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THE ERODE COLLEGE OF PHARMACY & RESEARCH INSTITUTE
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CERTIFICATE

This is to certify that the investigation in this thesis entitled **"Formulation and Evaluation of Chronomodulated Press-coated Pulsatile Therapeutic System for Carvedilol"** submitted to the Tamil Nadu Dr. M.G.R Medical University, Chennai, for the partial fulfillment of the award of Degree of **Master of pharmacy** in **Pharmaceutics,** was carried out by **Regd. No. 26105106** in the Department of Pharmaceutics. **The Erode College of Pharmacy and Research Institute**, **Erode-638112**.

This work is original and has not been submitted in part or full to any other degree or diploma of this or any other university.

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ENDORSEMENT BY THE PRINCIPAL

This is to certify that the investigation in this thesis entitled **"Formulation and Evaluation of Chronomodulated Press-Coated Pulsatile Therapeutic System for Carvedilol",** submitted in partial fulfillment for the award of degree of **Master of Pharmacy** in **Pharmaceutics,** were carried out in the laboratories of The Erode College of Pharmacy & Research Institute by **Reg. No. 26105106** under the guidance of **Dr. V. Gasesan, M. Pharm., PhD., Professor** in the Department of Pharmaceutics, The Erode College of Pharmacy and Research Institute, Erode 638112.

DECLARATION

The research work embodied in this dissertation work entitled "**Formulation and Evaluation of Chronomodulated Press-coated Pulsatile Therapeutic System for Carvedilol"** was carried out by me in **Department of Pharmaceutics, The Erode College of Pharmacy & Research Institute, Erode**, under the direct supervision of **Dr. V. Ganesan, M. Pharm., PhD., Professor** Department of Pharmaceutics, The Erode College of Pharmacy & Research Institute, Erode – 638112.

This dissertation submitted to The Tamil Nadu Dr. M. G. R. Medical University, Chennai, as a partial fulfillment for the award of degree of Master of Pharmacy in Pharmaceutics during the academic year 2011 – 2012.

The work is original and has not been submitted in part or full for the award for any other Degree or Diploma of this or any other University.

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Date: **Reg.No. 26105106**

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LIST OF ABBREVATIONS

% -Percentage

Kg– Kilogram

Gm – Gram

Mg – Milligram

µg – Microgram

ml– Millilitre

°C – Centigrade

Nm –Nanometer

µl – Microliter

CI –Carr's Index

Mm – Millimetre

UV – Ultra-violet spectrophotometer

HPMC –Hydroxypropyl methyl cellulose

MCC – Micro crystalline cellulose

Mins– Minutes

RH – Relative humidity

USP – United states pharmacopoeia

NF – National formulary

BP –British pharmacopoeia

ICH – International conference on harmonisation

#- Mesh

SD – Standard deviation

Abs – Absorbance

Cm – Centimetre

Con – Concentration

F - Formulation

PVP - ; polyvinylpyrrolidone

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INTRODUCTION

Many functions of the human body vary considerably in a day. These variations cause changes both in disease state and in plasma drug concentrations. Human circadian rhythm is based on sleep-activity cycle, is influenced by our genetic makeup and hence, affects the body's functions day and night (24-hour period) [48]. The dependence of bodily functions in certain disease states on circadian rhythm is well known. A number of hormones are released by the brain in the morning, while others are released during sleep. Blood pressure and heart rate are highest during the hours of 6.00 a.m. to 12.00 noon [49].

Diseases, such as hypertension, asthma, peptic ulcer, arthritis, etc, follow the body's circadian rhythm [50]. For example, osteoarthritis worsens during the day and is most bothersome in the evenings but for people with rheumatoid arthritis, the pain usually peaks in the morning and decreases as the day progresses. Cardiovascular diseases such as hypertension and angina, and chest pain, also follow a definite circadian rhythm. Epidemiologic studies have documented the heightened morning-time risk of angina, myocardial infarction, and stroke [51].

The goal in drug delivery research is to develop formulations to meet therapeutic needs relating to particular pathological conditions. Research in the chronopharmacological field has demonstrated the importance of biological rhythms in drug therapy, and this has brought a new approach to the development of drug delivery systems. Optimal clinical outcomes cannot be achieved if drug plasma concentrations are constant. If symptoms of a disease display circadian variation, drug release should also vary with time. Utilization of different technologies in the development of time-controlled, pulsed, triggered and programmed drug delivery devices has intensified in recent years.

Another issue that has emerged from circadian variation of physiological function is that drug pharmacokinetics can be time dependent (i.e., chronopharmacokinetics) [52]. Therefore, variation in disease state and drug plasma concentration need to be taken into consideration in the development of drug delivery systems intended for the treatment of diseases with adequate dose at the appropriate time. The term,

'Chronopharmaceutic drug delivery system', is used to describe a kind of drug formulation which can cause circadian variation in drug plasma levels [53,54.55].

CHRONOTHERAPEUTICS

The term "chrono" basically refers to the observation that every metabolic event undergoes rhythmic changes in time. Researchers have concluded that all living organisms are composites of rhythms with varying frequencies that may range from seconds to seasons. Perhaps the best known and studied chronobiologic frequency is the circadian rhythm which approximates the earth's 24-hour rotation around the sun [56]. Researchers have recently concluded that both disease states and drug therapy are affected by a multitude of rhythmic changes that occur within the human body [50].

Chronotherapeutics refers to a treatment method in which *in vivo* drug availability is timed to match rhythms of disease in order to optimize therapeutic outcomes and minimize side effects. It is based on the observation that there is an interdependent relationship between the peak-to-trough rhythmic activity in disease symptoms and risk factors, pharmacologic sensitivity, and pharmacokinetics of many drugs [58]. As more continues to be learned about chronobiology and chronotherapeutics, it is becoming increasingly more evident that the specific time that patients take their medication may be even more significant than was recognized in the past. The tradition of prescribing medication at evenly spaced time intervals throughout the day, in an attempt to maintain constant drug levelsthroughout a 24-hour period, may be changing as researchers' report that some medications may work better if their administration is coordinated with day-night patterns and biological rhythms.[48].

Diseases and chronotherapeutics

Up to now, design of drug delivery systems has been governed by the homeostatic theory [59]. This theory is based on the assumption of biological functions that display constancy over time. However, chronobiological studies have established circadian rhythm for almost all body functions, e.g., heart rate, blood pressure, body temperature, plasma concentration of various hormones, gastric pH and renal function [60]. It has become apparent that rhythmic processes are indispensable for the treatment of human diseases. Just as physiological functions vary over time,

pathological states of disease have circadian rhythms. Epidemiological studies have documented the elevated risk of disease symptoms during the 24-hour cycle (see Fig.) [61].

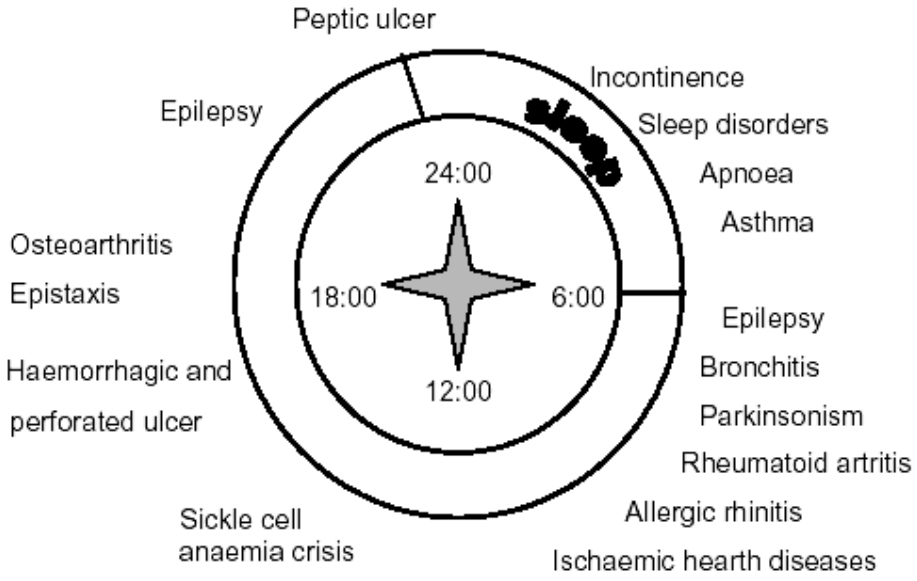


Figure 1: Diseases ln own to display circadian rhythm

The potential benefits of chronotherapeutics have been demonstrated in the management of a number of diseases. In particular there is a great deal of interest in how chronotherapy can particularly benefit patients suffering from allergic rhinitis, rheumatoid arthritis and related disorders, asthma, cancer, cardiovascular diseases, and peptic ulcer disease [50]. Patients with allergic rhinitis often report that they suffer their worst symptoms when they wake up in the morning. Patients may obtain better results in controlling this morning discomfort if they were to take a long-acting antihistamine at night rather than taking the medication in the morning as is frequently recommended [48].

Anti-inflammatory therapy

In the case of individuals who suffer from rheumatoid arthritis and related painful joint disorders, the non-steroidal anti-inflammatory agents (NSAIDs) such as ibuprofen may be more effective at relieving pain, if the drug is administered at least 4 to 6 hours before the pain reaches its peak. It will be more helpful if arthritis patients take the NSAIDs before bed time if they experience a particularly high level of discomfort in the morning . [61].

Anti-asthma therapy

It has been estimated that symptoms of asthma occur 50 to 100 times more often at night than during the day [62]. Many circadian-dependent factors appear to contribute to the worsening of nocturnal asthmatic symptoms. For example, cortisol (an anti-inflammatory substance) levels were highest at the time of awakening and lowest in the middle of the night, and histamine (a mediator of bronchoconstriction) concentrations peaked at a level that coincided with the greatest degree of bronchoconstriction at 4:00 am [50]. A research finding also reveals that theophylline absorption is slower at night [47]. The enhanced understanding of the chronobiological impact upon the pathology of asthma, and the pharmacology and pharmacokinetics of the drugs used in its management, have led to new approaches to disease management and enhanced patient care.

Chemotherapy

Antineoplastic drugs cause cytotoxic effects on healthy and diseased tissues. As would be expected, the biological rhythms of both healthy and tumor cells may influence the susceptibility of normal and malignant cells to these agents [62]. It has been demonstrated that "susceptibility rhythms" to drugs may differ between healthy tissue and cancerous tissue. Therefore, the "correct" timing of drug treatment may reduce host toxicity, increase maximum drug tolerance, and ultimately result in better tumor management. The pharmacologic and pharmacokinetic properties of the drug, rhythmic changes in DNA and RNA synthesis, RNA translational activity and mitotic activity may influence tumor cell susceptibility [50]. It appears that the timing of drug administration in the treatment of cancer can have a significant impact upon treatment success.

Cardiovascular therapy

The differences in patterns of illness between day and night for cardiovascular disorders such as hypertension, angina, heart attack, sudden cardiac death and stroke have been documented [48]. Medications have been formulated, and dosing schedules established, in an attempt to provide appropriate concentration of a drug in the target area of the body when the drug is most needed[48]. For example, it has often been found that the blood pressure of a hypertensive patient increases rapidly in the morning after awakening, typically peaks in the middle to late time of the

day, decreases in the evening, and is lowest while the patient sleeps at night [48]. It may also be important to recognize that the risk of heart attack appears to be greatest during the early morning hours after awakening. Currently, there are antihypertensive products in the market that are chronotherapeutic medications with novel drug delivery systems, releasing drug during the vulnerable period of 6 am to noon upon administration of medications at 10 pm. Some of these are listed in Table 1.

Table 1: Some chronotherapeutic antihypertensive products

Product	Generic name	Manufacturer
InnoPran XL	Propranolol	GlaxoSmithKline USA
Cardizem LA	Diltiazem	Biovail Corporation Mississauga, ONCanada
Verelan PM	Verapamil	Schwars Pharma Monheim, Germany
Covera HS	Verapamil	G. D. Searle (a division of Pfizer),NY, USA

Anti-ulcer therapy

It is well established that patients with peptic ulcer disease often experience the greatest degree of pain near the time that they go to bed, as the rate of stomach acid secretion is highest at night [48]. The timing of administration of ulcer medications has a significant impact on their therapeutic effect.

CHRONOPHARMACOKINETICS

Chronopharmacokinetics entails the study of temporal changes in drug absorption, distribution, metabolism and excretion [63]. Pharmacokinetic parameters, which are conventionally considered to be constant in time, are influenced by various physiological functions displaying circadian rhythm. Circadian changes in gastric acid secretion, gastrointestinal motility, gastrointestinal blood flow, drug protein binding, liver enzyme activity, renal blood flow and urinary pH may play a role in time-dependent variation of drug plasma concentration [63-65]. Numerous chronopharmacokinetic studies have been conducted over the last 20 years [63-66]. The results of these studies demonstrate that time of administration affects drug kinetics. Studies in man have been reported, particularly in relation to cardiovascular active drugs, non-steroidal anti-inflammatory drugs (NSAIDs), local anaesthetics, anticancer drugs, psychotropic drugs, antibiotics and anti-asthmatic

drugs [64]. Most of the drugs seem to have a higher rate or extent of bioavailability when they are taken in the morning than when they are taken in the evening.

Anti-hypertensive drugs

For example, with cardiovascular drugs such as nifedipine, oral nitrates and propranolol, plasma peak concentration is twice as high and time to reach peak concentration is shorter after morning dosing compared with evening dosing [63]. Such a variation was not detected when sustained release dosage forms of nifedipine and isosorbide mononitrate were used. The underlying mechanisms of their chronopharmacokinetic pattern involve a faster gastric emptying time and a greater gastrointestinal perfusion in the morning. Shiga *et al* documented that atenolol, in contrast to propranolol, is not absorbed more rapidly after morning administration compared with post-evening administration [66]. This confirms that the absorption rate of a lipophilic, but not hydrophilic, drugs is faster after morning dosing [67].

Anti-inflammatory drugs

Studies on NSAIDs, e.g., indomethacin and ketoprofen, have also shown that these drugs have a greater rate and/or extent of bioavailability when they are given in the morning than when they are given in the evening. Markedly higher ketoprofen plasma peaks were observed after administration at 07:00 than after administration at other times [68]. Earlier and higher peak concentrations were obtained when indomethacin was given at 07:00 or 11:00 than at other times of the day or night [69]. Better morning absorption has also been observed with controlled release indomethacin and ketoprofen formulations [70,71]. The clinical relevance of such variations is that high plasma concentrations correlate with high incidence of adverse effects. It has been suggested that morning absorption for these drugs is better than night-time absorption. Greater blood flow of the gastrointestinal tract in the morning than in the evening may explain this phenomenon. Circadian changes in renal function, plasma protein binding or hepatic blood flow could also explain temporal variation in drug plasma levels. Many variables are known to influence pharmacokinetics. In chronopharmacokinetic studies, it is important to strictly control the time of drug administration. When symptoms of the disease are circadian-dependent or drug used has a narrow therapeutic range, a

chronophannacokinetic study should be performed. The studies should be conducted under controlled conditions, including fasting time, composition of meals and posture.

CHRONOTHERAPEUTIC DRUG DELIVERY SYSTEMS

Controlled release formulations can be divided into subgroups of rate-controlled release, delayed-release and pulsed-release formulations. Delayed-release formulations include time-controlled release and sitespecific dosage forms [73-75]. When constant drug plasma levels need to be avoided, as in chronotherapy, time-controlled or pulsed-release formulations are preferable, especially in the treatment of early morning symptoms. By timing drug administration, plasma peak is obtained at an optimal time and the number of doses per day can be reduced. Saturable first-pass metabolism and tolerance development can also be avoided [75]. Various technologies to develop timecontrolled peroral drug delivery systems have been extensively studied in recent decades. Some of these systems are discussed in the following subsections.

Enteric-coated systems

Enteric coatings have traditionally been used to prevent the release of a drug in the stomach (see Fig 2). Enteric coatings are pHsensitive and drug is released when pH is raised above 5 in the intestinal fluid. These formulations can be utilised in time-controlled drug administration when a lag time is needed. Because of the unpredictability of gastric residence, such systems cannot be the first choice when a time-controlled release is required. In the treatment of nocturnal asthma, a salbutamol formulation containing a barrier coating which is dissolved in intestinal pH level above about 6, has been successfully used [76]. The system contains a core which is film coated with two polymers, first with HPMC and then with a gastro-resistant polymer (Eudragit® L30D). In this system the duration of the lag phase in absorption can be controlled by the thickness of the HPMC layer.

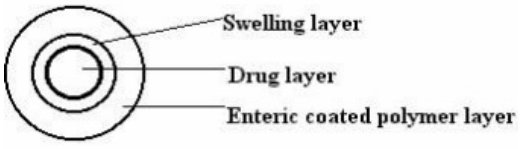


Figure 2: Schematic representtion of enteric coated system

Layered systems

These are one or two impermeable or semipermeable polymeric coatings (films or compressed) applied on both sides of the core [77]. To allow biphasic drug release, a three layer tablet system was developed [72]. The two layers both contain a drug dose. The outer drug layer contains the immediately available dose of drug. An intermediate layer, made of swellable polymers, separates the drug layers. A film of an impermeable polymer coats the layer containing the other dose of drug. The first layer may also incorporate a drug-free hydrophilic polymer barrier providing delayed (5 h) drug absorption. Conte *et al* has also studied a multi-layer tablet system (Geomatrix®). It consists of a hydrophilic matrix core containing the drug dose. This kind of three layer device has been used in the treatment of Parkinsonian patients using L--dopa/benserazide [78]. Night-time problems and early-morning symptoms of Parkinsonism can be avoided by using a dual-release Geomatrix@ formulation, which allows daily doses of drug to be reduced and leads to extent of bioavailability 40 % greater than when a traditional controlled release formulation is employed.

Time-controlled explosion systems (TES)

These have been developed for both single and multiple unit dosage forms [79, 80] . In both cases, the core contains the drug, an inert osmotic agent and suitable disintegrants. Individual units can be coated with a protective layer and then with a semipermeable layer, which is the rate controlling membrane for the influx of water into the osmotic core. As water reaches the core, osmotic pressure is built up. The core ultimately explodes, with immediate release of the drug. The explosion of the formulation also be achieved through the use of swelling agents. Lag time is controllable by varying the thickness of the outer polymer coating.

Sigmoidal release systems (SRS)

For the pellet-type multiple unit preparations, SRS containing an osmotically active organic acid have been coated with insoluble polymer to achieve different lag-times [81-83]. By aplying different coating thicknesses, lag times *in vivo* of up to 5 hours can be achieved. Release rates from SRS, beyond the lag time, has been found to be independent of coating thickness.

Press-coated systems

Delayed-release and intermittent-release formulations can be achieved by press--coating. Press-coating, also known as compression coating, is relatively simple and cheap, and may involve direct compression of both the core and the coat, obviating the need for a separate coating process and the use of coating solutions. Materials such as hydrophilic cellulose derivatives can be used and compression is easy on a laboratory scale. On the other hand, for large-scale manufacture, special equipment is needed. The major drawbacks of the technique are that relatively large amounts of coating materials are needed and it is difficult to position the cores correctly for the coating process [84].

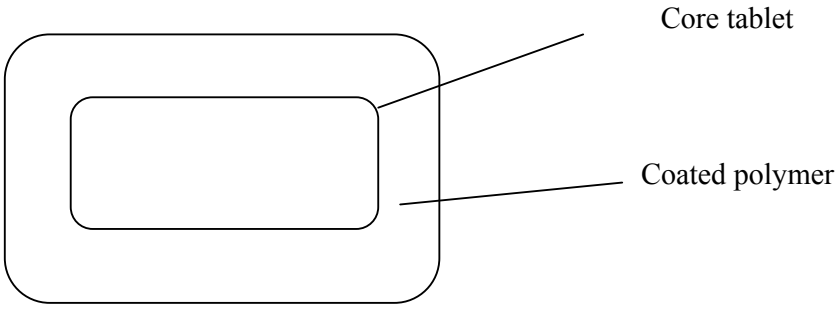


Figure 3: Schematic representation of a press coated system

In recent years, various controlled release, especially time-controlled release, drug delivery systems based on compression coating technology have been studied. Most of such formulations release drug after a lag phase, followed by a rapid dissolution of the core. Conte *et al* have developed a presscoated device in which the inner core contains the drug and the outer coat is made of different types of polymers. The outer barrier, which controls drug release, can be either swellable or erodible. Lag times can be varied by changing the barrier formulation or the coating thickness [5,7]. Matsuo *et al* have developed a diltiazem hydrochloride formulation intended for use in the treatment of time-related symptoms of ischaemic heart disease and hypertension [85]. The tablet consists of a core, which contains the drug, and a coat formed by compressing hydroxyethylcellulose. Diltiazem is rapidly released after a delay of several hours. Marvola *et al* have developed a press-coated tablet formulation in which most of the total amount of drug is in the tablet core [86]. Hydrophilic polymers such as hydroxypropyl methylcellulose and sodium alginate have been used in the coat to control drug

release as illustrated in Fig. 3. The extent of bioavailability of furosemide, ibuprofen and salbutamol sulphate from the system developed has been found to be satisfactory [92-95].

Other systems

Elementary osmotic pumps can be useful for delivering drugs based on chronotherapeutic requirements. One type of elementary osmotic pump can deliver salbutamol, initially at a constant delivery rate, then as a final pulse dose [96]. Such a system could deliver a dose during a nocturnal asthma attack. The first chronotherapeutic system for the treatment of hypertension and angina pectoris, a controlled onset extended-release (COER-24) verapamil formulation, was developed and registered in USA [97,98]. This formulation was tailored to the circadian rhythm of blood pressure and heart rate to better cover early morning symptoms of cardiovascular diseases. COER-24 is an osmotically controlled single unit system. Around the device, which consists of a drug layer and a push layer, are two membranes. The first is a semi-permeable insoluble membrane while the second is a release delaying hydrophilic polymer coat. Gastrointestinal fluid penetrates the semipermeable membrane, and as it enters the drug layer and push layer via the hydrated coat (within 4 to 5 hours), the push layer expands, pressing against the drug layer and causing drug release at a constant rate for 18 hours. If taken at bedtime, the system provides optimal drug concentration when the patient wakes up and during day time.

Pulsinocapo is a delivery system which releases drug contents at a predetermined time or at a specific site within the gastrointestinal tract [99]. Each capsule is composed of a water insoluble body and a water soluble cap, and also contains the drug dose which is sealed with a hydrogel plug. At a predetermined time after ingestion, the swollen plug is ejected from the capsule and the drug is then released into the small intestine or colon. The dimension of the plug and its position in the capsule can be varied and the system delivers drug at exactly the programmed time, 1 to 10 hours after drug administration, to various regions of the gut.

LITERATURE REVIEW

V. S. Chopra *et al*, (2010)[1] Studied applicability of chronotropic or pulsatile drug delivery systems to release the drug at desired time as per the pathophysiological need of disease, resulting in improved patient therapeutic efficacy and complianceine. Chronotropic drug delivery systems are promising in treatment of asthma, peptic-ulcer, cardiovascular diseases, arthritis, attention-deficit syndrome in children and hypercholestemia etc.

Andrea Gazzaniga, Alessandra Maroni and Maria Edvige Sangalli *et al*, (2009)[5] Developed pulsatile-release dosage forms to elicit programmable lag phases followed by a prompt or rate-controlled liberation of drugs for accomplishing chronotherapeutic goals, particularly in the case of widespread chronic pathologies with prevailing night or early-morning symptoms, such as bronchial asthma and cardiovascular disease. Delayed liberation of drugs has been attained through a range of formulation approaches, namely reservoir, capsular and osmotic release platforms.

Dhruvita K. Pate *et al*, (2011) Studied Purpose of Pulsatile drug delivery is to release drugs on a programmed pattern at appropriate time and/or at appropriate site of action. Pulsatile drug delivery systems administered via the oral route could be divided into two types, the time controlled delivery systems and the site-specific delivery systems. The simplest pulsatile formulation is a two layer press coated tablet consisted of polymers with different dissolution rates. Homogeneity of the coated barrier is mandatory in order to assure the predictability of the lag time.

B.U Janugade *et al, (*2009)[2] Formulated montelukast sodium compression/press-coated pulsatile drug delivery system by using direct compression and wet granulation methods to achieve the predetermined lag time. Different compositions of hydrophobic polymer ethylcellulose and hydrophilic polymer low-substituted hydroxypropylcellulose were mixed to formulate the whole layer of the outer shell of press coated tablets. They conclude that lag time decreases with increasing

concentration of low substituted hydroxypropylcellulose and wet granulation method gives less lag time.

Parag A. Kulkarni *et al,* (2010)[3] Studied applicability of press coated tablet with optimal lag time to simulate the dosing time of drug administration according to the pathophysiological needs. They formulated Diltiazem hydrochloride, as core and different compositions of klucel HF, klucel HXF, Eudragit RSPO were mixed to formulate the outer shell. They conclude that Diltiazem hydrochloride, released maximum drug 6 to 8 hours after an evening dose taken approximately 10:00 pm.

Shan-Yang Lin, Mei-Jane Li, and Kung-Hsu Lin *et al*, (2004)[4] Formulated the compression/dry-coated tablet with optimal lag time to simulate the dosing time of drug administration according to the physiological needs. Different compositions of ethylcellulose powder with a coarse particle and several fine particles respectively were mixed to formulate the whole layer of the outer shell of dry-coated tablets. They conclude that sodium diclofenac released from all the dry-coated tablets exhibited an initial lag period, followed by a stage of rapid drug release.

N. Kanaka Durga Devi *et al*, (2010)[6] Developed and evaluated press coated tablet of Montelukast sodium in order to overcome disadvantages like first pass metabolism, peak and valley absorptions at different absorption sites and drug instability problems. Besides that, to treat Nocturnal asthma (NA), diseases which show dependency on chronopharmacology. They conclude that Montelukast sodium based on press coating technique has worthy effects in treating NA as well as to curtail extensive first pass metabolism of the drug.

Mayur M. Patel, Santnu L. Patel, Manish N. Bhadani, *et al*, (2009)[7] Formulated pH-dependent mesalamine Pulsatile drug delivery system. It is designed such that the innermost part consists of a core tablet of mesalamine which is then compression coated with a pH-independent hydrophilic polymer (Hydropropylmethyl cellulose). This is then coated with a pH-dependent

methacrylic acid copolymer (Eudragit® S100). The concentration (coating level) of Eudragit® S100 was optimized to provide an enteric coat that allows the tablet to pass intact through the stomach and is targeted to the colon. The coating thickness and grades of HPMC were optimized to set a desired lag time in the intestine. From the in vitro evaluation it can revealed that the developed CDDS can exhibit site-specific drug targeting to the colon.

Sumit Patil *et al*, (2011)[9] Formulated aceclofenac press-coated pulsatile drug delivery system for treatment of early morning stiffness and symptomatic relief from pain in patients with rheumatoid arthritis. The formulation involved press coating of a rupturable coat around a rapidly disintegrating core tablet of aceclofenac, Different compositions of glyceryl behenate, sodium chloride were mixed to formulate the coating layer of the outer shell, to investigate the influence of coating material on lag time. They conclude that Glyceryl behenate had a significant influence on lag time, while sodium chloride helped in the rupture of the coat by acting as a channelling agent. After the coat was ruptured, the core tablet showed a rapid release of aceclofenac.

B.G. Prajapati, G.N. Patei, H.K. Solanki *et al*, (2010)[10] Formulated Propranolol hydrochloride compression coated tablet using 3^2 full factorial Design, to evaluate statical influence different concentration of hydroxy propyl methyl cellulose K4M and ethyl cellulose on lag time to simulate the dosing time of drug administration according to the physiological needs. They conclude that formulation F3 exhibited best initial lag period, followed by rapid release of drug.

J Sajan, TA Cinu, AJ Chacko, J Litty and T Jaseeda *et al*, (2009)[11] Developed pulsatile-release dosage forms to elicit programmable lag phases followed by a prompt or rate-controlled liberation of drugs for accomplishing chronotherapeutic goals, particularly in the case of widespread chronic pathologies with prevailing night or early-morning symptoms, such as bronchial asthma and cardiovascular disease. Delayed liberation of drugs has been attained through a range of formulation approaches, namely reservoir, capsular and osmotic release platforms.

Ashish Babulal Rane *et al*, (2009) Formulated pulsatile drug delivery of ketoprofen using hydrophilic and hydrophobic polymer for accomplishing chronotherapeutic needs of rheumatoid arthritis patient. Different weight ratio of hydrophobic and hydrophilic polymer where mixed to formulate outer coating shell to exhibited an initial lag period, followed by a stage of rapid drug release.

Richard J. Martin, MD, **Monica Kraft, *et al.*, (1995)**[12] investigated in Chronobiology and Chronotherapy in Respiratory medicine. It was found that, Chronotherapeutic delivery of theophylline, once daily in the evening between 6 p.m & 7 p.m controls Asthma nocturnal symptoms and early morning bronchoconstriction. This regimen has been found to be clinically superior to conventional twice-daily dosing.

Eiji Fukui*, Katsuji Uemura, *et al.*, (2000)[13] Studied on applicability of press-coated tablets using hydroxypropylcellulose (HPC) in the outer shell for timed-release preparations. It contains diltiazem hydrochloride (DIL) in the core tablet and coated with hydroxypropylcellulose (HPC) as the outer shell, was examined for applicability as timed-release tablets with a predetermined lag time and subsequent rapid drug release phase. Two different kinds of timed-release press-coated tablets that showed lag times of 3 and 6 h in the *in vitro* test (denoted PCTL3 and PCTL6 respectively) were administered to beagle dogs. The lag times showed a good agreement between the *in vivo* and *in vitro* tests in PCTL3. However, the *in vivo* lag times were about 4 h in PCTL6 and were much shorter than the *in vitro* lag time.

Michael H. Smolensky, Nicholas A. Peppas *et al.*, (2007)[14] Investigated on Chronobiology, drug-delivery and chronotherapeutics. chronotherapeutics is the delivery of medications in the right concentration to the right targeted tissues at the right time to meet biological rhythm-determined needs. Many chronic and acute medical conditions exhibit prominent circadian patterns of symptom manifestation and severity. Among the many examples are allergic rhinitis, bronchial asthma, and peptic ulcer disease; all tend to worsen overnight. The risk of many cardiovascular

events, like angina pectoris, myocardial infarction, and thrombotic and hemorrhagic stroke, is greatest in the morning. The content of these articles clearly makes apparent many potential new applications of existing drug-delivery systems and devices, and it serves also as the basis for future developments.

Sarasija Suresh, **H.N. Shivakumar, *et al., (*2006)**[15]** Studied on design and evaluation of controlled onset extended release multiparticulate systems for chronotherapeutic delivery of Ketoprofen. It consists of drug-loaded cellulose acetate cores encapsulated with in Eudragit S-100 microcapsules was designed for chronotherapeutic delivery of ketoprofen. Drug-loaded cellulose acetate cores were prepared by emulsion solvent evaporation technique in an oily phase at different drug: polymer ratios (1:1, 2:1 and 4:1).these cores were successfully microencapsulated with Eudragit S-100 following the same technique at the core: coat ratio of 1:5. SEM revealed that the cellulose acetate cores were discrete, uniform & spherical. The aim was to minimize drug release in the upper part of the GI tract and target the drug to the colon.

Mukai B., Utoguchi N *et al.,* (2002)[16] Prepared and evaluated the press-coated Aminophylline tablet using crystalline cellulose and PEG in the outer shell for timed-release dosage forms. The core tablet is prepared by direct compression method using rotary tablet punching machine. Press coating of core tablets using different ratios of crystalline cellulose and PEG. Tablets are evaluated for *In vitro* dissolution test showed a lag time of 6 hours.

Martti Marvola *et al.,*(2001)[17] Studied the development and biopharmaceutical evaluation of press-coated tablets with the intention of administering formulation in the evening at 22:00, which provides treatment for diseases in which symptoms are experienced in the early morning hours i.e**.** chronopharmacotherapy. The focus is to optimally deliver the drug in higher amounts in early morning hours (i.e. at time of greatest need) and lower amounts at night (i.e. when the need of drug is less).

Michael Prisant .L *et al.* (2001)[18] Reported on Biologic rhythms are implicated in cardiovascular events. Failure to recognize the circadian decline in blood pressure may result in iatrogenic chronopathological events, including anterior ischemic optic neuropathy and cerebrovascular accidents. Novel drug delivery systems have the potential to provide antihypertensive medication at the time when the need is greatest. For the treatment of hypertension, this idea has the potential for a therapeutic paradigm shift Chronotherapeutics is the purposeful alteration of drug level to match rhythms to optimize therapeutic outcomes and minimize size effects for the treatment of hypertension.

Ramon C. Hermida, Diana E. Ayala, *et al.,* (2007)[26], studied on Chronotherapy of hypertension: valsartan administration at bedtime, as opposed to upon wakening, results in an improved diurnal/nocturnal BP ratio, increased percentage of controlled patients, and significant reduction in urinary albumin excretion in hypertensive patients. Chronotherapy provides a new option to optimize BP control and to reduce the risk of cardiovascular disease (myocardial infarction and stroke) and of end-organ injury of the blood vessels and tissue of the heart, brain, kidney, eye, and other organs.

Qureshi.J, Mohd, Sanjula Baboota, *et al.,*(2006)[27], investigated on Pulsatile drug delivery system having a peculiar mechanism of delivering the drug rapidly & completely after a "lag time". i.e., a period of "no drug release" though most delivery systems are designed for constant drug release over a prolonged period of time, constant blood levels of a drug may not always desirable. Pulsatile systems are designed in a manner that the drug is available at the site of action at the right time in the right amount.

D. Searle. LLC, *et al.,*(2006)[28], Covera-HS has a unique controlledonset extended-release (COER) delivery system, which is designed for bedtime dosing, results in a maximum plasma concentration (Cmax) of verapamil in the morning hours. Covera-HS was evaluated in two placebo-controlled, parallel design, doubleblind studies of 382 patients with mild to moderate hypertension. In a clinical trial, 287 patients were randomized to placebo, 120 mg, 180 mg, 360 mg, or 540 mg and treated for 8 weeks (the two higher doses were titrated from low

doses and maintained for 6 and 4 weeks, respectively). Covera-HS or placebo was given once daily at 10 pm and blood pressure changes were measured with 36-hour ambulatory blood pressure monitoring (ABPM). The results of these studies demonstrate that Covera-HS, at 180–540 mg, is a consistently and significantly more effective antihypertensive agent than placebo in reducing ambulatory blood pressures.

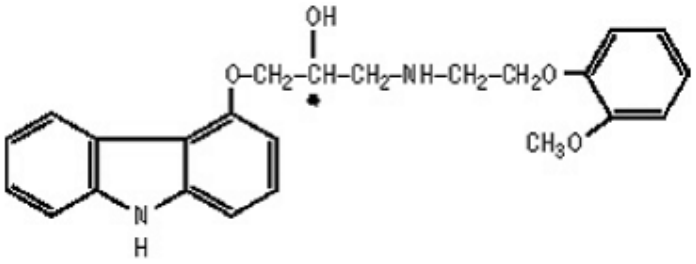
DRUG PROFILE

Carvedilol: [41]

Description: It is a non – selective beta blocker; it blocks β-1 and β-2 adrenergic receptors as well as the α-1 adrenergic receptors. It is a white or almost white, crystalline powder.

Chemical Name: (2RS)-1-(9 H-carbazol-4-yloxy)-3-[2-(2-methoxyphenoxy) ethyl] amino] propan-2-ol

Chemical Structure:



Molecular Formula : $C_{24}H_{26}N_2O_4$

Molecular Weight : 406.5 g/mole

Melting point : 114 - 115^{0}C.

Solubility : It is easily soluble in dimethyl sulfoxide (DMSO), also easily soluble in methanol and methelene chloride, isopropranolol, ethyl ether and ethanol can partially dissolve. Practically insoluble in water.

Dose : 25mg twice a day in the treatment of congestive heart failure.

Elimination half life : 6 - 8 hours

Bioavailability : 25 - 35%

PHRMACOKINETICS: [42.]

Absorption

i.) Non-genetic

a. Food: decreases rate (not extent) of absorption

b. Age : 50% increase in bioavailability in elderly (increased plasma concentrations)

c. Liver disease: oral bioavailability significantly increased

d. Concomitant medications/substances: p-glycoprotein inhibitors

ii.) Genetic

a. Genetic variation in p-glycoprotein gene

Distribution

i.) Non-genetic

a. Liver disease: 4-fold increase in volume of distribution

b. Altered serum protein (>95% protein bound, primarily to albumin)

c. Concomitant medications/substances: p-glycoprotein inhibitors or activators

ii.) Genetic

a. Genetic variation in p-glycoprotein gene

Metabolism

I) Non-genetic

a. Congestive heart failure (CHF): 30-40% higher plasma concentrations

b. Liver impairment

i. 4- to 7-fold higher concentrations in cirrhotic liver disease

ii. Contraindicated in severe hepatic impairment

c. Concomitant medications/substances: CYP2C9**,** CYP2D6**,** CYP3A4, CYP2C19, CYP1A2, CYP2E1inducers or inhibitors

II) Genetic

a. Genetic variation in drug metabolizing enzyme gene(s): CYP2C9**,** CYP2D6**,** CYP3A4, CYP2C19, CYP1A2, CYP2E1

Excretion

i.) Non-genetic

a .Renal impairment: increased plasma concentrations

b .Renal impairment + hypertension: markedly increased plasma concentrations

c. 50% shorter elimination half-life in paediatrics (ages 6 weeks – 19 years) with CHF

d. Age: Elimination half-life increases with age in paediatrics

ii.) Genetic

a. No clear genetic factors affecting excretion.

PHRMACODYNAMICS:

Receptors

i.) Non-genetic

a. Concomitant medications: alpha- or beta-adrenergic receptor agonists/antagonists (may block or enhance therapeutic effects of carvedilol)

ii.) Genetic

a. Genetic variation in beta-1 adrenergic receptor gene

b. Genetic variation in alpha-1 adrenergic receptor gene

c. Genetic variation in Gs protein alpha subunit gene

Transporters

i.) Non-genetic

Concomitant medications/substances: p-glycoprotein inhibitors or activators.

ii.) Genetic

Genetic variation in p-glycoprotein gene.

SIDE EFFECTS AND PRECAUTIONS:

Dizziness, Edema (fluid accumulation), decreased heart rate, diarrhea, postural hypotension, irregular heart rhythm, abnormalities of vision. Carvedilol should be used cautiously in patients who use diuretics or who are elderly or have cirrhosis, asthma, peripheral vascular disease, hyperthyroidism, variant angina and kidney disease.

CONTRAINDICATIONS: It is contraindicated during pregnancy.

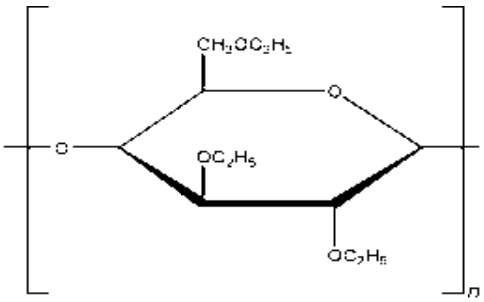
EXCIPIENT PROFILE

ETHYLCELLULOSE:[19]

Description: Ethyl cellulose is a tasteless, free-flowing, white to light tan colored powder.

Chemical Name: Cellulose ethyl ether.

Chemical Structure:



Functional Category : Coating agent, flavoring fixative, tablet binder, tablet filler. **Viscosity**: increasing agent.

Solubility: Soluble in chloroform, ethanol (95%), ethyl acetate, methanol, and toluene. Practically insoluble in glycerin, propylene glycol and water.

Bulk density	**:**	0.4 g/cm^3
Viscosity	**:**	7 to 100 mPa s for 5% w/v solutions
Specific gravity	**:**	1.12–1.15 g/cm^3

Stability: Ethyl cellulose is a stable, slightly hygroscopic material chemically resistant to alkalis (both dilute and concentrated) and to salt solutions, although it is more sensitive to acidic materials than are cellulose esters.

Incompatibility: Incompatible with paraffin wax and microcrystalline wax.

Application:

1) The main use of ethyl cellulose in oral formulations is as a hydrophobic coating agent for tablets and granules.

2) Ethyl cellulose coatings are used to modify the release of a drug, to mask an unpleasant taste, or to improve the stability of a formulation; for example, where granules are coated with ethyl cellulose to inhibit oxidation.

3) Modified-release tablet formulations may also be produced using ethyl cellulose as a matrix former

Safety: Ethyl cellulose is widely used in oral and topical Pharmaceutical formulations. It is also used in food products.

HYDROXY PROPYL METHYL CELLULOSE 4000:[19]

Non Proprietary Name:

BP	**:**	Hypermellose
PhEur	**:**	Methylhydroxypropylcellulosum
USP	**:**	Hydroxypropyl methyl cellulose

Synonyms: Cellulose, hydroxypropyl methyl ether, methocel, ethylcellulose propylene glycol ether, methyl hydroxyl propylcelluloes metolose, pharmacoat.

Description: Hydroxypropyl methylcellulose is an odourless and tasteless white or creamy white coloured fibrous or granular powder.

Chemical Name: Cellulose, 2-Hydroxypropyl methyl ether.

Functional Category: Coating agent, film former, stabilizing agent, suspending agent, tablet binder, viscosity increasing agent.

Empirical Formula: The PhEur describes HPMC as a partly O-methylated and o-(2-hydroxypropylated) cellulose. It is available in several grades which vary in viscosity and extent of substitution. HPMC defined in the USP XXII specifies the substitution type by appending a four digit number to the non proprietary name, e.g., hydroxypropyl methylcellulose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH_3). The second two digits refer to the approximate percentage content of the hydropropoxy group ($OCH_2CHOHCH_3$).

Tapped Density **:** 0.05-0.70g/cm^3 for pharmacoat.

Melting Point **:** Browns at 190-200^{0}C, chars at 225-230^{0}C.

Solubility: Soluble in cold water, forming a viscous colloidal solution, practically insoluble in chloroform, ethanol (95%) and ether, but soluble in mixtures of ethanol and dichloromethane.

Stability and Storage: HPMC is a stable material although it is hygroscopic after drying. Solutions are stable between pH 3-11. Increasing temperature reduces the viscosity of solution. The gel point is 50-90^{0}C depending upon the grade of material. HPMC powder should be stored in a well-closed container, in a cool, dry place.

Incompatibilities: It is incompatible with some oxidizing agents. Since it is non-ionic, hydrolxypropyl methylcellulose will not complex with metallic salt and ionic organics to form insoluble precipitates.

Applications: Widely used in oral and topical pharmaceutical formulations. In oral products, it is primarily used as a tablet binder, in film coating and as an extended release tablet matrix. Concentrations of between 2-5% w/w may be used as a binder in either wet or dry granulation processes. It is also used a suspending agent and thickening agent in topical formulations, particularly ophthalmic preparations. Used as adhesive in plastic bandages and as wetting agent for hard contact lenses.

GUGAR GUM[19]

Non proprietary names:

BP	:	Guar galactomannan
PhEur	:	Guar galactomannum
USPNF	:	Guar gum

Synonyms: E412; Galactosol; guar flour; jaguar gum; meprogat; meprodor; meyprofin; meyproguar.

Chemical name and CAS Registry number: Galactomannan polysaccharide [9000-30-0]

Empirical formula : $(C6H12O6)_n$

Molecular weight : ≈ 220000

Structural formula: Guar gum consists of linear chains of (1→4)-β-D-mannopyranosyl units with α-D-galactopyranosyl units attached by (1→6) linkages. The ratio of D galactose to D-mannose is between 1:1.4 and 1:2

Description: The USPNF 20 describes guar gum as a gum obtained from the ground endosperms of cyamopsis tetragonolobus (Fam: Leguminosae).

Colour	**:**	white to yellowish white
Odour	**:**	odorless or nearly odourless
Taste	**:**	bland taste
Texture	**:**	powder
Acidity / Alkalinity	**:**	pH 5.0 to 7.0 (1% w/v aqueous dispersion)
Viscosity	**:**	4.86 Pas for 1% w/v dispersion

Solubility: In organic solvents disperses and swells immediately in cold or hot water to form a highly viscous and thixotropic solution.

Functional category: Suspending agent, Tablet binder, Tablet disintegrant, Viscosity increasing agent

Applications in pharmaceutical technology:

1) Used in solid dosage forms as a binder (up to 10%) and disintegrant

2) Used in oral and topical products as a suspending, thickening (up to 2.5%) and stabilizing agent (1%)

3) Used in colon targeted drug delivery systems

4) Used as an appetite suppressant

5) Also, used in cosmetic and food products

Storage: Guar gum should be stored in a well closed container and kept in a cool and dry place.

Incompatibilities: It is incompatible with acetone, alcohol, tannins, strong acids and alkalis. Presence of borate ions in distilled water, will prevents the hydration of guar gum.

MICROCRYSTALLINE CELLULOSE [19]

Nonproprietary names:

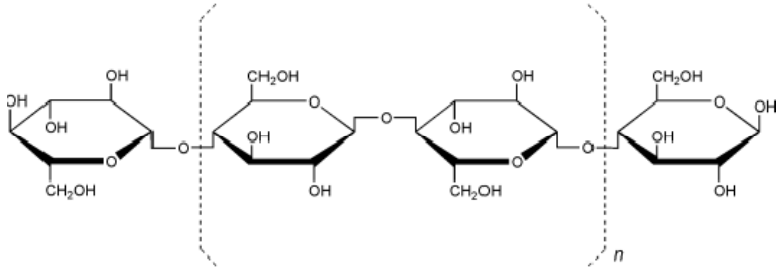
BP	:	Microcrystalline cellulose
JP	:	Microcrystalline cellulose
PhEur	:	Cellulosum microcristallinum
USPNF	:	Microcrystalline cellulose

Synonyms: Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; Pharmacel; Tabulose; Vivapur.

Chemical name and CAS Registry number: Cellulose [9004-34-6]

Empirical formula and molecular weight: $(C_6H_{10}O_5)_n$ ≈36 000. Where n ≈ 220.

Structural Formula:



Functional Category: Adsorbent; Suspending agent; Tablet and Capsule Diluent; Tablet Disintegrant.

Applications in pharmaceutical formulation or technology: Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet granulation and direct-compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting. Microcrystalline cellulose is also used in cosmetics and food products.

Description: Microcrystalline cellulose is purified, partially depolymerised cellulose that occurs as a white, odourless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Typical properties:

Solubility: Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

Stability and storage conditions: Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities: Microcrystalline cellulose is incompatible with strong oxidizing agents.

Safety: Microcrystalline cellulose is widely used in oral pharmaceutical formulations and food products and is generally regarded as a relatively nontoxic and non irritant material. Microcrystalline cellulose is not absorbed systemically following oral administration and thus has little toxic potential. Consumption of large quantities of cellulose may have a laxative effect, although this is unlikely to be a problem when cellulose is used as an excipient in pharmaceutical formulations. Deliberate abuse of formulations containing cellulose, either by inhalation or by injection, has resulted in the formation of cellulose granulomas.

POLYVINYL PYRROLIDONE[20]

Nonproprietary Names:

BP : Povidone

USP : Povidone

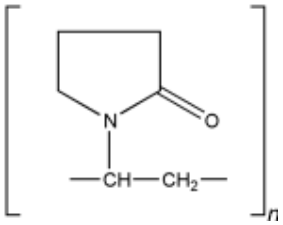
Synonyms: Kollidon: Plasdone, polyvidone; polyvinylpyrrolidone, PVP.

Chemical Name and CAS Registry Number: 1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

Empirical Formula: (C6H9NO) n

Molecular Weight*:* 2500–3 000 000

Structural Formula:



Functional Category: Disintegrant; dissolution aid; suspending agent; tablet binder.

Description: Povidone occurs as a fine, white to creamy-white colored, odourless or almost odourless, hygroscopic powder. Povidones with K-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres.

Typical Properties:

Solubility: Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water,

the concentration of a solution is limited only by the viscosity of the resulting solution.

Incompatibilities: Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It forms molecular adducts in solution with Sulfathiazole, Sodium Salicylate, Salicylic Acid, Phenobarbital, Tannin, and other compounds. The efficacy of some preservatives, e.g. thiomersal, may be adversely affected by the formation of complexes with Povidone.

Applications in Pharmaceutical Formulation or Technology: Although Povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. In tabletting, Povidone solutions are used as binders in wet-granulation processes. Povidone is also added to powder blends in the dry form and granulated in situ by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms. Povidone solutions may also be used as coating agents.

TALC

Synonyms: Altalc; E553b; Hydrous Magnesium Calcium Silicate; Hydrous Magnesium Silicate; Luzenac Pharma; Magnesium Hydrogen Metasilicate; Magsil Osmanthus; Magsil Star; Powdered Talc; Purified French Chalk; Purtalc; Soapstone; Steatite; Superiore.

Chemical Name and CAS Registry Number: Talc [14807-96-6]

Empirical Formula and Molecular Weight: Talc is a purified, hydrated, magnesium silicate, approximating to the formula $Mg_6(Si_2O_5)_4(OH)_4$. It may contain small, variable amounts of aluminium silicate and iron.

Functional Category: Anticaking agent; Glidant; Tablet and Capsule Diluent; Tablet and Capsule Lubricant.

Applications in Pharmaceutical Formulation or Technology: Talc was once widely used in oral solid dosage formulations as a lubricant and diluents.

Description: Talc is a very fine, white to grayish-white, odourless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Moisture content: Talc absorbs insignificant amounts of water at 25°C and relative humidities up to about 90%.

Solubility: Practically insoluble in dilute Acids and Alkalis, Organic Solvents, and Water.

Stability and Storage Conditions: Talc is a stable material and may be sterilized by heating at 160°C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities: Incompatible with quaternary ammonium compounds.

MAGNESIUM STEARATE

Physico chemical properties

Description: Magnesium stearate is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Molecular Weight : 591.34

Structural Formula: CH3 (CH2)16COO] 2Mg

Crystalline forms : High-purity magnesium stearate has been isolated as a trihydrate, a dihydrate, and an anhydrate.

Flowability : poorly flowing, cohesive powder.

Melting range : 117–150°C (commercial samples)126–130°C (high purity magnesium stearate)

Solubility: Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Specific surface area: 1.6–14.8 m^2/g

Functional Category: Tablet and capsule lubricant**.**

Applications in Pharmaceutical Formulation Technology: It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w.

Incompatibilities: Incompatible with strong acids, alkalis, and iron salts. Strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

AIM AND PLAN OF WORK

The main objective of the present study was to develop Compression coated tablets of carvedilol for Chronotherapeutic delivery. Carvedilol is used in the treatment of hypertension and angina pectoris. According to circadian rhythm (24hr- Biological clock) the Blood pressure (BP) will be more in early morning 3a.m – 6a.m because rennin, cortisol, angiotensin, aldosterone secretion is in peak level, most of the cardiovascular disorders such as Angina pectoris, sudden cardiac death, stroke, occurs at this time, the designed formulation to be taken at bed time and the focus is to optimally deliver the drug in higher amounts in early morning hours (i.e. at time of greatest need) and lower amounts at night (i.e. when the need of drug is less).

Carvedilol is a highly lipophilic drug and is almost completely absorbed after oral administration. However, its bioavailability is very limited (25% to 35%) due to the hepatic first-pass effect. Its elimination half-life is also relatively short (about 6–8 h). Therefore, it was chosen as a model drug for preparation of the once-daily controlled extended release dosage form. An oral time controlled release formulation facilitates the administration, just once a day to control the BP in patient with morning surge, which results in better compliance by patients and fewer side effects. The present work was undertaken with the aims to achieve time-controlled release with distinct predetermined lag time by using hydrophobic and hydrophilic polymers.

EXPERIMENTAL DESIGN

Table 2: Materials used:

SR NO	MATERIALS	MANUFACTURERS/ SUPPLIERS
1.	Carvedilol	Shasun Pharmaceuticals Ltd., Pondicherry.
2.	Ethyl Cellulose	S.D. Fine Chem. Ltd., Mumbai
3.	Hydroxy Propyl Methyl Cellulose 4000	Ajantha Pharma, Mumbai
4.	Polyvinylpyrrolidone	Ajantha Pharma, Mumbai
5.	Microcrystalline cellulose	Loba Chemi Pvt., Ltd., Mumbai
6.	Guar gum	Himedia Laboratories.
7.	Talc	S.D. Fine Chem. Ltd., Mumbai
8.	Magnesium Stearate	S.D. Fine Chem. Ltd., Mumbai.

Table 3: Equipment used:

S. NO.	INSTRUMENT	MANUFACTURER/SUPPLIER
1.	Electronic Balance	Sartorius, Germany.
2.	Rotary tablet Compression Machine (10 stages)	Rimek Mini Press I.
3.	Hardness Tester	Monsanto.
4.	Friability Test Apparatus	Roche friabilator.
5.	Vernier Calliper	Inox- Somet,Japan.
6.	Dissolution Apparatus.	Electro Lab. (USP XX III) (DTD – 06P).
7	Double BeamUV Spectrophotometer	Systronic Corporation, Mumbai.
8	FTIR Spectrophotometer	Perkin Elmer Spectrum, Japan.
10	Digital pH Meter	Eutech Instruments, Japan.
11	Hot Air Oven	Kemi, Mumbai.
12	Melting Point Apparatus.	Kemi, Mumbai.
13	Bulk Density Apparatus.	Kemi, Mumbai.

PREFORMULATION STUDIES

Before formulation of drug substances into a dosage form, it is essential that it should be chemically and physically characterized. Preformulation studies give the information needed to define the nature of the drug substance and provide a frame work for the drug combination with pharmaceutical excipient in the fabrication of a dosage form.

In the present work, preformulation studies on the development of calibration curve of the drug candidate and the compatibility between drug and excipient were carried out.

Development of calibration curve for carvedilol:[21]

Standard curve of carvedilol in acid buffer pH 1.2

Accurately weigh 100 mg and dissolved in acid buffer of pH 1.2 in a 100 ml volumetric flask and the solution was made up to the volume with acid buffer of pH 1.2 to give 1000µg/ml solution. From the above solution 10 ml was diluted to 100 ml using acid buffer of pH 1.2 to give 100µg/ml working stock solution. The above working stock solution was subsequently diluted with acid buffer of pH 1.2 to obtain a series of dilutions containing 1, 2, 3, 4 and 5 µg/ml of solution. The λmax of the drug was determined by scanning the dilutions between 400 and 200 nm using a double beam UV-visible spectrophotometer (Systronic). At this wavelength, the absorbance's of all the other solutions are measured using the acid buffer of pH 1.2 as blank. The concentrations of carvedilol and the corresponding absorbance values are given in table 14. The absorbance values were plotted against concentrations of carvedilol as shown in fig.1. The method obeys Beer-Lambert's law in the concentration range of 1-5 µg/ml.

Preparation of pH 1.2 Hcl acid buffer

Place 50 ml of the 0.2 M potassium chloride in a 200 ml volumetric flask, then add 85 ml of 0.2 M hydrochloric acid and then add distilled water to make up the volume.

Preparation of 0.2 M potassium chloride

Dissolve 14.911 gm of potassium chloride in 1000 ml of distilled water. This will give 0.2 M potassium chloride.

Preparation of 0.2 M hydrochloric acid

Place 7.292 gm (17.8 ml) of hydrochloric acid in 1000 ml of distilled water, this will give 0.2 M HCl acid

Table 4: Absorbance of carvedilol in acid buffer (pH 1.2)

Concentration (µg/ml)	Absorbance (nm)
1	0.194
2	0.360
3	0.562
4	0.729
5	0.905

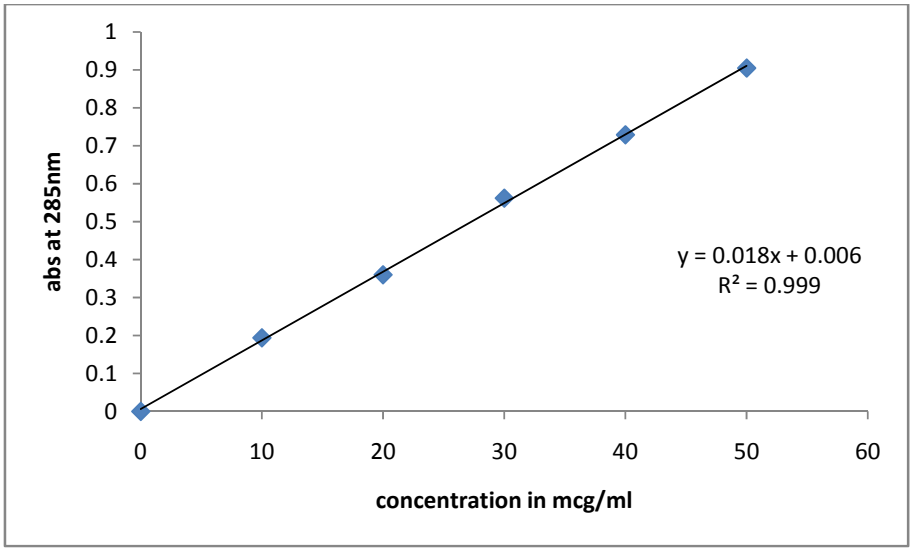


Fig .4 Standard curve of carvedilol in acid buffer (pH 1.2)

*Sl*ope = 0.0181

Correlation coefficient = .09994

Standard curve of carvedilol in phosphate buffer pH 6.8:

Accurately weigh 100 mg of carvedilol and dissolved in phosphate buffer of pH 6.8 in 100 ml volumetric flask and the solution was made up to the volume with phosphate buffer of pH 6.8 to give 1000 µg /ml solution. From the above solution 10 ml was diluted to 100 ml using phosphate buffer of pH 6.8 to give 100µg/ml working stock solution. The above working stock solution was subsequently diluted with phosphate buffer of pH 6.8 to obtain a series of dilutions containing 1, 2, 3, 4 and 5 µg/ml of solution. The λmax of the drug was determined by scanning the dilutions between 400 and 200 nm using a double beam UV-visible spectrophotometer (Systronic). At this wavelength, the absorbance's of all the other solutions are measured using the phosphate buffer of pH 6.8 as blank. The concentrations of carvedilol and the corresponding absorbance values are given in table 15. The absorbance values were plotted against concentrations of carvedilol as shown in fig.2. The method obeys Beer-Lambert's law in the concentration range of 1-5 µg/ml.

Preparation of pH 6.8 phosphate buffer

Place 50 ml of the 0.2 M potassium dihydrogen phosphate solution in a 200 ml standard volumetric flask and add 22.4 ml of 0.2M sodium hydroxide solution to this flask and make up the volume with distilled water.

Potassium dihydrogen phosphate, 0.2 M solution

Take accurately weighed 27.22 gm of Potassium dihydrogen phosphate and dissolved in 1000 ml of distilled water, this will give 0.2 M KH2PO4.

Sodium hydroxide 0.2 M solution

Take accurately weighed 8 gm of sodium hydroxide and dissolved in 1000 ml of distilled water, this will give 0.2 M NaOH solution.

Table 5: Absorbance of carvedilol in phosphate buffer (pH 6.8)

Concentration (µg/ml)	Absorbance (nm)
1	0.23
2	0.50
3	0.750
4	0.99
5	1.2

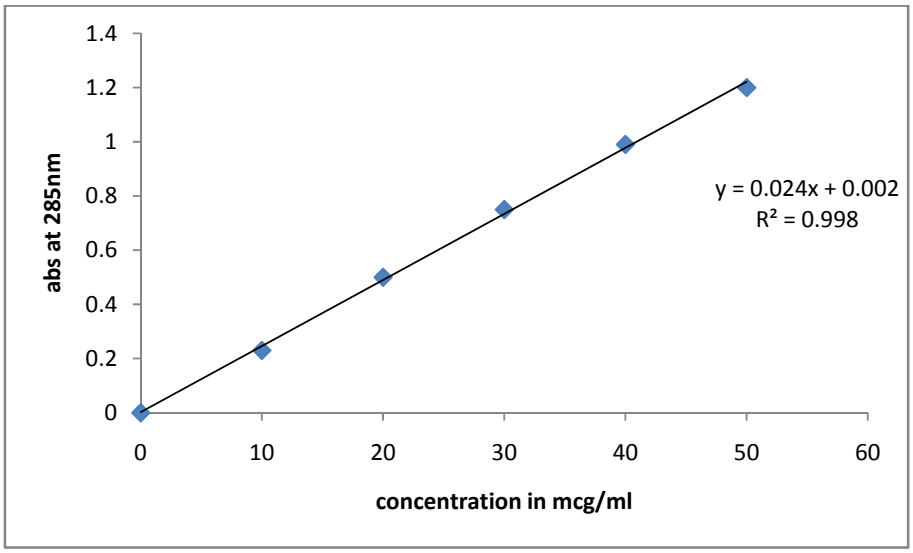


Fig.5 Standard curve of carvedilol in phosphate buffer (ph6.8)

Slope = 0.0244

Correlation coefficient = 0.9988

Drug-excipient compatibility studies[34]

In compression coated tablet formulation (in core) drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drugs. Preformulatin studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate polymer. FT-IR (Perkin Elmer Spectrum, Japan.). spectroscopy was employed to ascertain the compatibility between carvedilol and the selected polymer. The pure drug and drug with excipient were scanned separately scanned in the range 4000-400 cm^{-1} (drug :polymer 1:1). potassium bromide was mixed with drug and/or polymer (in ratio 1:100) and compressed under 10-ton pressure in a hydraulic press to form a transparent pellet. The pellet was scanned from 4000-400 cm^{-1} and the spectra were taken. FT-IR spectrum of carvedilol was compared with FT-IR spectra of carvedilol with polymer disappearance of carvedilol peaks or shifting of peak in any spectra was studied

Table 6: Assessment of the functional groups of carvedilol obtained in FT-IR spectra of compatibility studies.[47]

S. N	Functional group	Standard ir range cm^{-1}	Assesment peaks of pure drug cm^{-1}
1	Secondary amine (N-H stretching)	3500-3300	3344.68
2	Secondary alcohol	1350-1260	1305.85
3	Aromatic	3050-3000	3058.24
4	C-H	2960-2850	2923.22
5	Aromatic hydrocarbons	1600	1606.76
6	Disubstituted (ortho)	770-735	752.26
7	-OCH3 stretching	Below 3000	2923.22
8	C=C stretching in aromatic nuclei	1700-1400	1449.55, 1504.53, 1589.40, 1606.76,1629.90

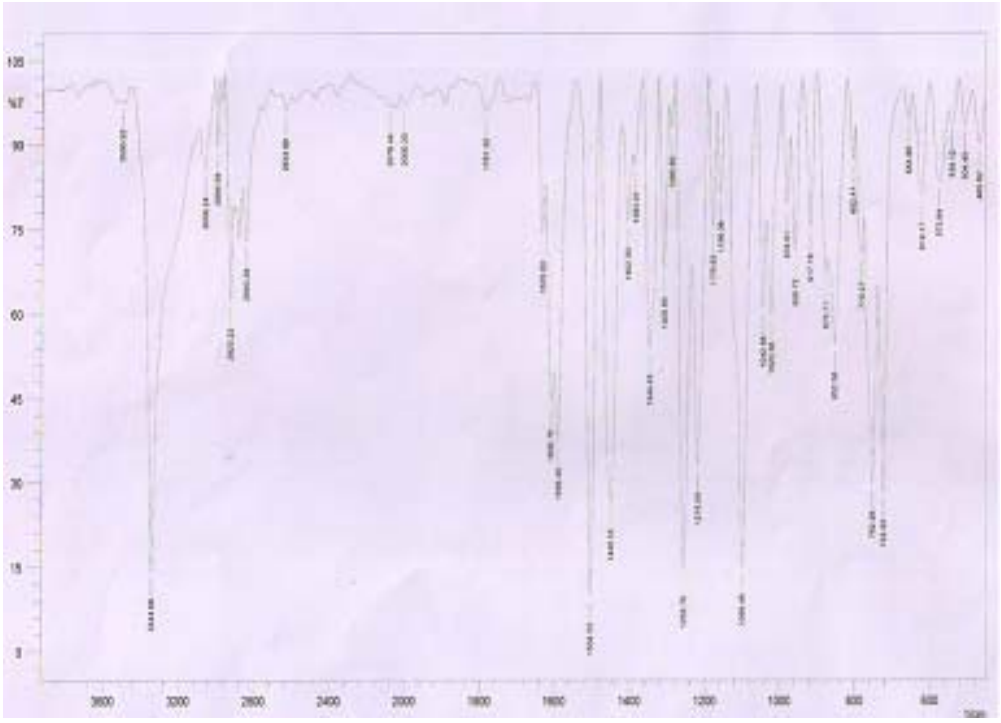


Fig. 6 FTIR spectra of pure drug

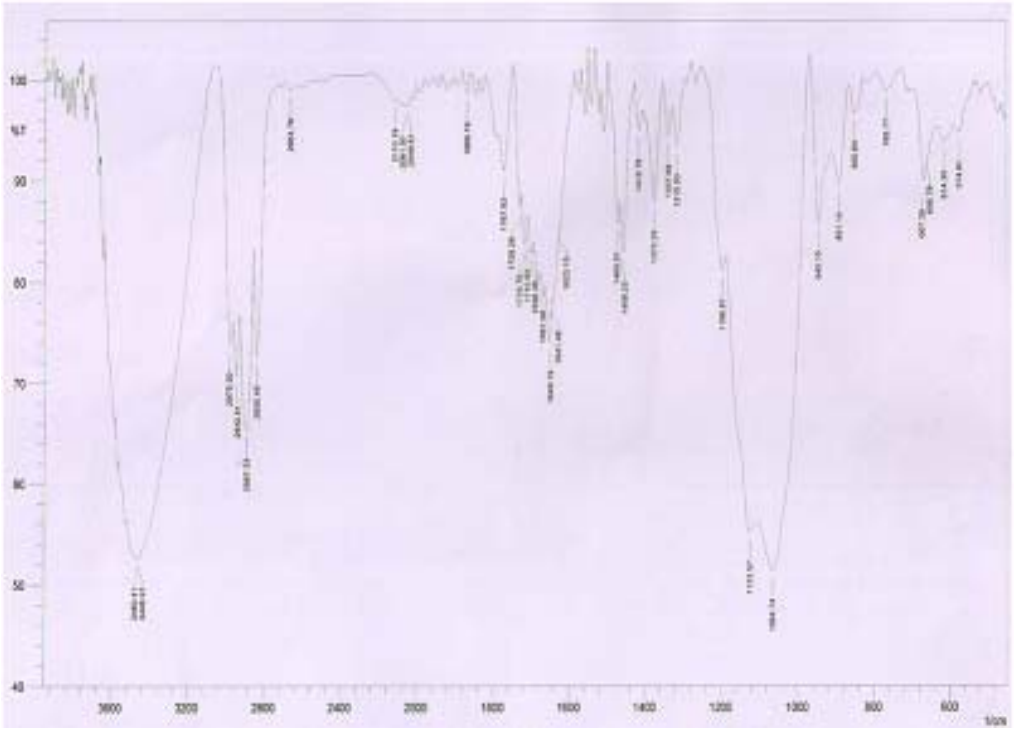


Fig. 7 FTIR spectra of HPMC 4000

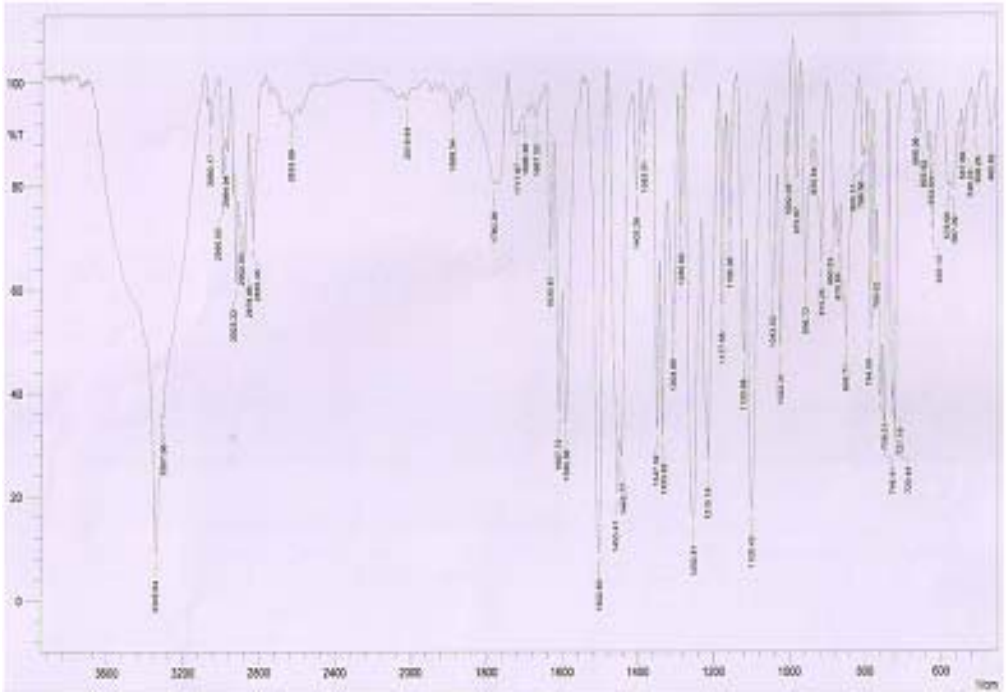


Fig. 8 FTIR spectra of pure drug +HPMC 4000

Precompression Parameters : [22, 23, 29, 30, 31`, 32]

Angle of repose: The flow property of the powder drug was determined by measuring the Angle of Repose. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal plane. Values of θ are rarely less than 20^o, and values of up to 40^o indicate reasonable flow potential. Above 50^o, however, the powder flows only with difficulty if at all.

$$\theta = Tan^{-1} (h/r)$$

Where,

h is height the pile.

r is radius of the pile.

θ is angle of repose.

A funnel was fixed in a holder; the tip of the funnel was placed at a height of 6 cm from the surface. A graph sheet was placed below the funnel. 5 gms of the sample were taken and were passed slowly through the funnel. The height of the powder heap formed was measured. The circumference of the heap formed was drawn with a pencil on the graph paper. The radius was determined and the angle of response

was determined using the given formula. The same procedure was repeated 3 times for each sample.

Determination of bulk density and tapped density: 20 g of the powder (W) from each formula was introduced individually into a 100ml of measuring cylinder. After that the initial volume was noted, the cylinder was kept in bulk density apparatus for tapping. The tapping was continued for 100 times and the change in volume was noted.

The bulk density, and tapped density were calculated using the following formulas: -

$$\textbf{Bulk density} = W / V_0$$

$$\textbf{Tapped density} = W / V_f$$

Where,

W is weight of the powder.

V_0 is initial volume.

V_f is final volume.

The results were presented in the table:7

Compressibility index (Carr's index): Compressibility index is an important measure which can be obtained from bulk and tapped densities. Theoretically, the less compressible a material the more flowable it is.

This shows that a material having value of less than 18 % is defined as the free flowing material.

$$C_I = 100 (V_0 - V_f) / V_0$$

Where,

C_I is compressibility index.

Haussner's Ratio: This indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density.

$$\text{Hauser's Ratio} = (W / V_f) / (W / V_0)$$

Where,

W / V_f = Tapped density.

W / V_0 is Bulk density.

Thus,

Haussner's Ratio = Tapped density/Bulk density.

Table 7: precompression parameters of core tablets F1-F9

Formulation code	Angle of repose	Bulk density (gm/cm^2)	Tapped density (gm/cm^2)	Compressibility index (%)	haussner's ratio
F1	24.07	0.660	0.625	18.98	1.03
F2	21.84	0.530	0.585	17.24	1.05
F3	23.98	0.516	0.592	19.51	1.19
F4	24.63	0.484	0.579	19.11	1.16
F5	24.41	0.464	0.606	15.99	1.18
F6	23.14	0.457	0.597	11.41	1.12
F7	25.32	0.502	0.516	14.39	1.08
F8	26.26	0.499	0.619	12.40	1.16
F9	24.31	0.506	0.721	17.58	1.17

Table 8: Precompression parameters of coated material powder blend F1-F9

Formulation Code	Angle of Repose	Bulk Density (gm/cm^2)	Tapped Density (gm/cm^2)	Compressibility Index (%)	Haussner's Ratio
F1	$23^0$14"	0.740	0.869	14.814	1.174
F2	$25^0$42"	0.714	0.800	10.714	1.120
F3	$24^0$33"	0.689	0.769	10.344	1.116
F4	$25^0$45"	0.769	0.869	11.538	1.130
F5	$26^0$38"	0.714	0.833	14.285	1.166
F6	$24^0$34"	0.689	0.800	13.793	1.161
F7	$23^0$44"	0.769	0.869	11.538	1.130
F8	$26^0$36"	0.740	0.833	11.111	1.125
F9	$24^0$44"	0.714	0.833	14.285	1.166

Formulation of Compression -Coated tablets of Carvedilol[40, 43]

The different formulations of carvedilol controlled onset extended release tablets were formulated by press-coating technique under direct compression method using a combination of hydrophobic polymer ethylcellulose, hydrophilic polymer polyvinylpyrrolidone, and natural swellable polymer guar gum as outer coating layer.

Formulation of Core Tablets

The core tablets containing drug, HPMC and MCC, were prepared by weighing all the ingredients and passed through sieve no.80 and mixed in a geometrical dilution method. Magnesium stearate and talc (1% each) were added to each blend and further mixed. The resultant blends were tableted to 60 mg using 7/32 flat punches in a rotary tabletting machine (Rimek minipress, India).

Compression -Coating of Core Tablet

The composition of the tablets is given in Table 9. Ethyl cellulose (EC) and each mixture of polyvinylpyrrolidone and guar gum were passed through a sieve no.80 and 90 mg of the powder mixture was used for the outer shell. Different weight

ratios of (w/w) of EC/excipient mixture were formulated as shown in Table 7 & 8. The press-coating of tablets was performed using 9/32 concave punches in a rotary tabletting machine (Rimek minipress, India). A half amount of the EC/excipient mixture was filled into the die to make a powder bed, on the centre of which was placed the core tablet. Then, the remaining half of the EC/excipient mixture was filled in the die and the contents were compressed to prepare the compression-coated tablet.

The hydrophilic gums are extensively used for oral extended release dosage forms due to their simplicity, cost effectiveness and reduction of the risk of systemic toxicity due to dose dumping. Furthermore, pH-independent drug release is preferable for oral extended release formulations, so as not to be affected by intra- and inter-subject variations of both gastric pH and GI transit time. The hydroxypropylmethylcellulose (HPMC) is a pH-independent material and the drug release rates from HPMC matrix formulations are generally independent of processing variables such as compaction pressure, drug particle size, and the incorporation of a lubricant .Therefore, HPMC is widely used to prepare extended release dosage forms.

Table 9: The composition and formulation code for various tablets containing Carvedilol

S. No.	Ingredients mg/tab	Formulation code								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Carvedilol	25	25	25	25	25	25	20	30	25
2.	HPMC	20	20	20	20	20	20	20	20	35
3.	Microcrystalline Cellulose	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
4.	Ethyl cellulose	45	60	30	45	60	30	45	45	45
5.	PVP	45	30	60	_	_	_	45	45	45
6.	Guar gum	_	_	_	45	30	60	_	-	_
7.	Magnesium Stearate	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
8.	Talc	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Table 10: The composition and formulation code of various Compression coated tablet containing Carvedilol using EC & PVP outer coat.

S. NO.	Formulation Code	EC	PVP	In ratios
1	F1	45	45	1:1
2	F2	60	30	2:1
3	F3	30	60	1:2
4	F7	45	45	1:1
5	F8	45	45	1:1
6	F9	45	45	1:1

Table 11: The composition and formulation code of various PCT containing Carvedilol using EC & guar gum as outer coat.

S. NO	FormulationCode	EC	Guar gum	In ratios
1	F4	45	45	1:1
2	F5	60	30	2:1
3	F6	30	60	1:2

EVALUATION OF CORE AND PRESS COATED TABLET:[24]

The above core and press coated tablet were evaluated for physical properties like: Thickness, Hardness, Friability, Weight variation, Drug content uniformity, Compatibility studies and *In vitro* dissolution studies

Tablet Thickness: The thickness of the tablet was measured with Vernier Calliper. Three tablets were selected from each formulations and the test was performed.

Hardness Test: Hardness test was carried out by using "Monsanto" hardness tester. Three tablets were randomly selected from each of the formulations and the test was carried out.

Friability Test: "Roche" friabilator is used to determine the friability of the tablets. For determining the friability of the tablets six tablets were taken and weighed. After weighing the tablets were placed in the Roche friabilator and was allowed for the combined effects of abrasion and shock by utilizing a plastic chamber which was then allowed to revolve at 25 rpm for 4 minutes, this drops the

tablets from a height of six inches with each revolution. After undergoing this procedure the tablets were dedusted and reweighed.

Friability can be determined by

$$F = 100 (1-W_t/W_o)$$

Where,

W_o is weight of tablets before friability test.

W_t is weight of tablets after friability test.

Weight Variation Test: Ten tablets were selected at random and the average weight was determined. Not more than two of the individual tablet's weights should deviate from the average weight by more than the percentage deviation shown in table and none should deviates by more than twice the percentage.

Table 12: Standard data of percentage deviation of tablets as per USP

Pharmaceutical Form	Average mass	% Deviation
Tablets	≤130 mg	± 10
	> 130 mg - 324 mg	± 7.5
	≥ 325 mg	± 5

$$\% \text{ Maximum positive deviation} = (W_H - A/ A) \times 100$$

$$\% \text{ Minimum negative deviation} = (A-W_L/ A) \times 100$$

Where,

W_H is highest weight in mg.

W_L is lowest weight in mg.

A is average weight of tablet in mg.

Drug Content of Core Tablets: Five tablet from each batch was powdered individually and a quantity equivalent to 25 mg of Carvedilol was weighed and dissolved in a suitable volume of phosphate buffer (6.8 pH). After making suitable

dilutions the absorbance of the solution was measured against the corresponding blank at 285 nm using a double beam UV/Visible spectrophotometer

Table 13: Evaluation of Core-Tablet

S No	Formulation code	Hardness (kg/cm2)	Friability (%)	Average thickness in mm	weight variation mg	%Drug content
1	F1	3.1	0.355	1.89	61	91.66
2	F2	2.9	0.361	2.1	60	99.33
3	F3	3.0	0.328	1.95	60	93.66
4	F4	2.8	0.289	2.11	61	93.66
5	F5	2.9	0.321	1.99	58	94.33
6	F6	3.1	0.310	1.94	59	96.33
7	F7	2.8	0.348	1.90	61	92.66
8	F8	3.0	0.308	2.0	59	95.00
9	F9	3.2	0.360	2.14	58	94.00

Table 14: Evaluation of press coated tablet containing carvedilol using EC/PVP as an outer coat

S. No.	Formulation Code	Hardness (kg/cm2)	Friability (%)	Average thickness in mm	weight variation mg
1	F1	5.1	0.14	3.22	153
2	F2	5.2	0.19	3.30	152
3	F3	5.4	0.06	3.32	153
4	F7	5	0.14	3.58	150
5	F8	4.9	0.56	3.27	154
6	F9	5.7	0.56	3.35	155

Table 15: Evaluation of press coated tablet containing Carvedilol using EC/Guar gum as an outer coat.

S. No.	Formulation Code	Hardness (kg/cm2)	Friability (%)	Average thickness in mm	weight variation mg
1	F4	5.6	0.03	3.52	154
2	F5	5.3	0.11	3.46	151
3	F6	5.4	0.09	3.37	153

***In vitro* drug release study of press coated tablets**[40] *In-vitro* dissolution studies were performed on nine different press coated tablets prepared by direct compression method at $37^{o} \pm 0.5$ °C using 900 ml of acid buffer (1.2 pH) for two hours followed by 900 ml of phosphate buffer (6.8 pH) as dissolution media for twenty two hours in USP apparatus II with the paddle speed 50 rpm. 5 ml of filtered aliquot was withdrawn at pre-determined time intervals (1,2,3,4,5,6,7,8,12,16,20,24 hours) and replaced with 5 ml of fresh 1.2 pH acid buffer and 6.8 pH phosphate buffer solution respectively, maintained at the same temperature. The samples were analyzed at 285 nm using a UV spectrophotometer. The amount of carvedilol dissolved in the dissolution media was then determined from the calibration curve. The lag time and percentage release of carvedilol was determined for the each formulation.

Details of dissolution test:

Dissolution test apparatus	:	USP type II
Speed	:	50 rpm
Stirrer	:	Paddle type
Volume of medium	:	900 ml
Aliquot taken at each time interval	:	5 ml
Medium used	:	Acid buffer (pH 1.2),
	:	Phosphate buffer (pH 6.8).
Temperature	:	$37 \pm 0.5\ ^{0}C$

Table 16: Percentage *In vitro* Release profileof Carvedilol containing EC/PVP/Guar gum using Various Buffers.

Time (hrs)	Percentage release of Carvedilol from PCT								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0	0	0	0	0	2.3	0	0	0
2	0	0	0	2.9	0	6.7	0	0	0
3	0	0	3.6	8.5	0	8.3	0	0	0
4	6.6	0	6.7	11.7	0	18.9	3.7	4.7	3.4
5	17.3	0	14.6	23.7	0	31.3	10.1	8.6	7.0
6	30.8	13.2	25.1	35.8	14.4	44.3	22.6	24.2	18.8
7	38.3	25.1	36.4	54.2	29.2	52.8	30.9	33.2	26.5
8	43.6	37.6	48.0	74.3	39.6	69.2	41.2	41.2	33.9
12	70.2	67.2	67.6	84.3	69.3	84.3	72.7	72.7	62.9
16	78.4	80.9	85.3	94.1	80.6	97.4	81.7	84.6	76.3
20	88.1	91.5	98.8	99.3	94.2	-	92.9	90.1	84.9
24	96.5	99.3	-	-	98.1	-	99.3	98.1	96.5

Table 17: Dissolution profile of formulation F1* containing Carvedilol using buffer pH 1.2 and 6.8

Time (hr)	Absorbance (290 nm)	Amount (µg/ml)	Amount (mg/900ml)	Cumulative %release
1	0.000	0	0	0
2	0.000	0	0	0
3	0.000	0	0	0
4	0.0453	1.85	1.67	6.68
5	0.1175	4.81	4.33	17.3
6	0.2084	8.54	7.68	30.88
7	0.2536	10.56	9.51	38.3
8	0.2922	11.97	10.77	43.6
12	0.4709	19.29	17.36	70.2
16	0.5242	21.48	19.33	78.48
20	0.5869	24.05	21.64	88.16
24	0.6402	26.23	23.61	96.5

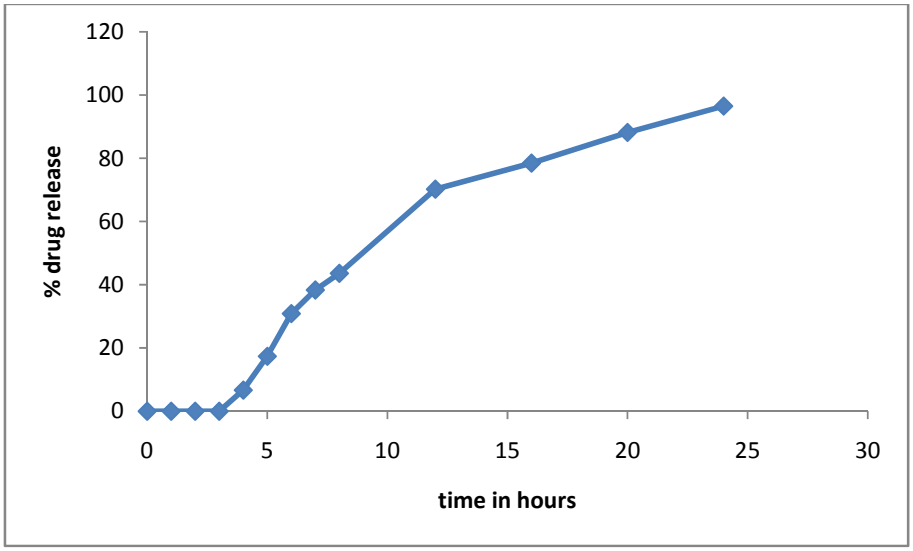


Fig 9 in vitro drug release profile of carvedilol F1 (EC:PVP1:1)

Table 18: Dissolution profile of formulation F2* containing carvedilol using buffer pH 1.2 and 6.8

Time (hr)	Absorbance (290 nm)	Amount (µg/ml)	Amount (mg/ 900ml)	Cumulative %release
1	0	0	0	0
2	0	0	0	0
3	0	0	0	0
4	0	0	0	0
5	0	0	0	0
6	0.09	3.68	3.31	13.27
7	0.17	6.96	6.27	25.15
8	0.2536	10.39	9.35	37.62
12	0.4532	18.57	16.71	67.28
16	0.5432	22.26	20.03	80.93
20	0.612	25.08	22.57	91.53
24	0.661	27.09	24.38	99.3

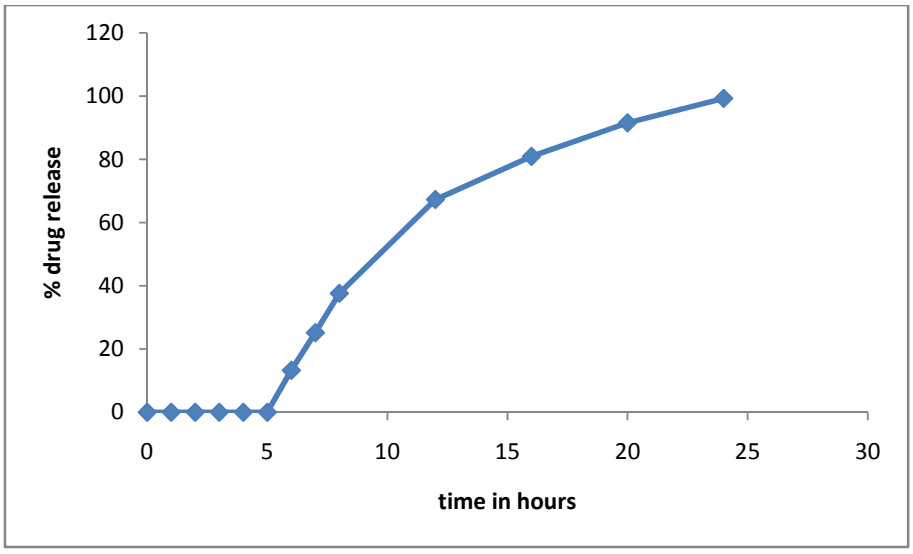


Fig. 10 in vitro drug release profile of carvedilol F2 (EC:PVP2:1)

Table 19: Dissolution profile of formulation F3* containing carvedilol using buffer pH 1.2 and 6.8

Time (hr)	Absorbance (290 nm)	Amount (µg/ml)	Amount (mg/900ml)	Cumulative %release
1	0	0	0	0
2	0	0	0	0
3	0.025	1.02	0.92	3.68
4	0.0453	1.85	1.67	6.70
5	0.099	4.05	3.65	14.66
6	0.1698	6.95	6.29	25.19
7	0.245	10.04	9.03	36.42
8	0.3224	13.21	11.89	48.04
12	0.4532	18.57	16.71	67.60
16	0.571	23.40	21.06	85.36
20	0.659	27.00	24.30	98.81
24	-	-	-	-

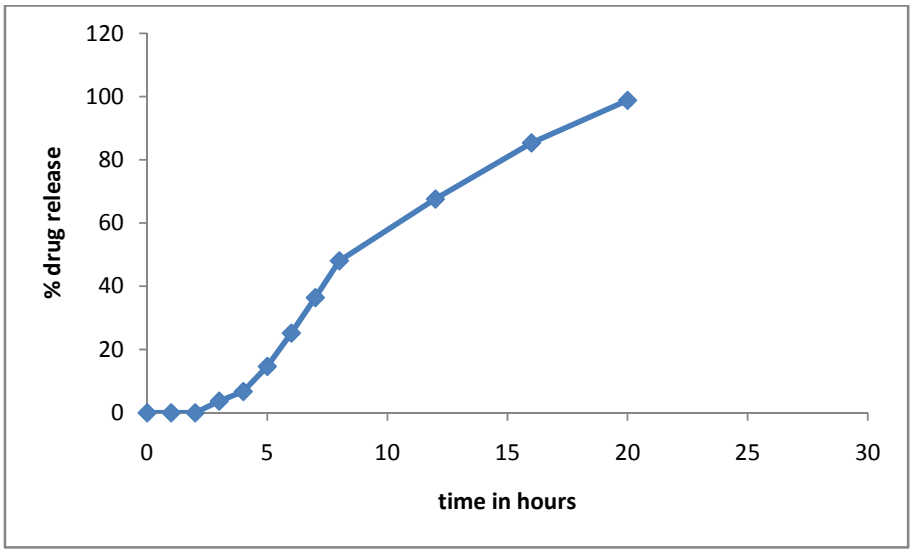


Fig. 11 In vitro drug release profile of carvedilol F3 (EC:PVP 1:2)

Table 20: Dissolution profile of formulation F4* containing carvedilol using buffer pH 1.2 and 6.8

Time (hr)	Absorbance (290 nm)	Amount (µg/ml)	Amount (mg/900ml)	Cumulative %release
1	0	0	0	0
2	0.0416	0.80	0.72	2.90
3	0.0579	2.37	2.13	8.55
4	0.0789	3.23	2.91	11.70
5	0.1598	6.54	5.89	23.70
6	0.241	9.87	8.88	35.81
7	0.3644	14.93	13.44	54.22
8	0.4988	20.44	18.39	74.34
12	0.564	23.11	20.80	84.37
16	0.627	25.69	23.12	94.13
20	0.659	27.00	24.84	99.3
24	-	-	-	-

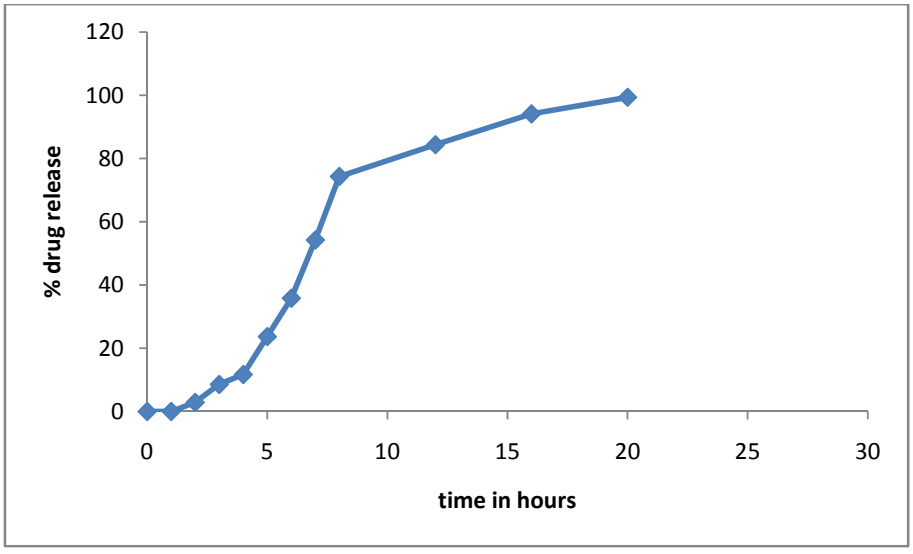


Fig. 12 in vitro drug release profile of carvedilol F4 (EC:GUAR 1:1)

Table 21: Dissolution profile of formulation F5* containing carvedilol using buffer pH 1.2 and 6.8

Time (hr)	Absorbance (290 nm)	Amount (µg/ml)	Amount (mg/900ml)	Cumulative %release
1	0	0	0	0
2	0	0	0	0
3	0	0	0	0
4	0	0	0	0
5	0	0	0	0
6	0.09	4.02	3.62	14.48
7	0.198	8.11	7.30	29.29
8	0.267	10.94	9.84	39.63
12	0.467	19.13	17.22	69.36
16	0.541	22.17	19.95	80.66
20	0.630	25.83	23.25	94.29
24	0.653	26.76	24.08	98.14

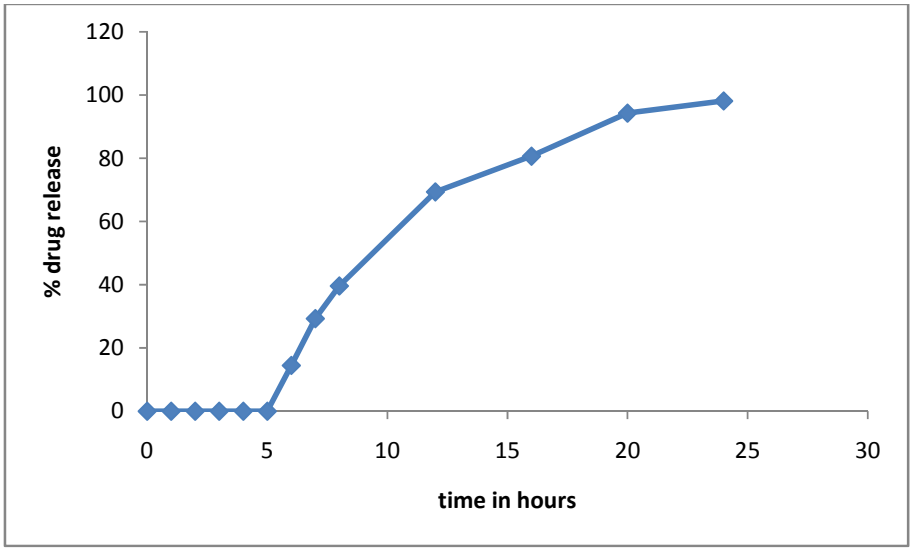


Fig.13 in vitro drug release profile of carvedilol F5 (EC:GUAR GUM 2:1)

Table 22: Dissolution profile of formulation F6* Containing carvedilol using buffer pH 1.2 and 6.8

Time (hr)	Absorbance (290 nm)	Amount (µg/ml)	Amount (mg/900ml)	Cumulative %release
1	0.012	0.66	0.59	2.38
2	0.0305	1.68	1.51	6.07
3	0.056	2.29	2.07	8.30
4	0.127	5.22	4.72	18.90
5	0.211	8.64	7.78	31.32
6	0.298	12.22	10.99	44.36
7	0.354	14.50	13.05	52.84
8	0.463	18.97	17.07	69.21
12	0.563	23.07	20.76	84.34
16	0.649	26.59	23.93	97.4
20	-	-	-	-
24	-	-	-	-

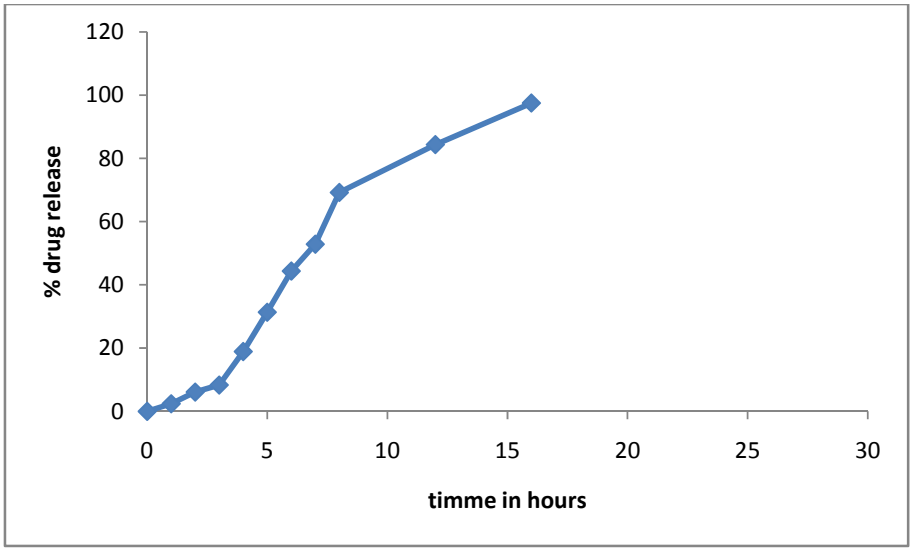


Fig.14 in vitro drug release profile of carvedilol F6 (EC:GUAR GUM 1:2)

Table 23: Dissolution profile of formulation F7* containing carvedilol using buffer pH 1.2 and 6.8

Time (hr	Absorbance (290 nm)	Amount (µg/ml)	Amount (mg/900ml)	Cumulative %release
1	0	0	0	0
2	0	0	0	0
3	0	0	0	0
4	0.025	1.03	0.93	3.73
5	0.068	2.82	2.54	10.18
6	0.153	6.27	5.64	22.65
7	0.208	8.54	7.68	30.95
8	0.277	11.36	10.22	41.27
12	0.489	20.04	18.18	72.74
16	0.547	22.41	20.42	81.70
20	0.62	25.40	23.23	92.92
24	0.66	27.04	24.34	99.33

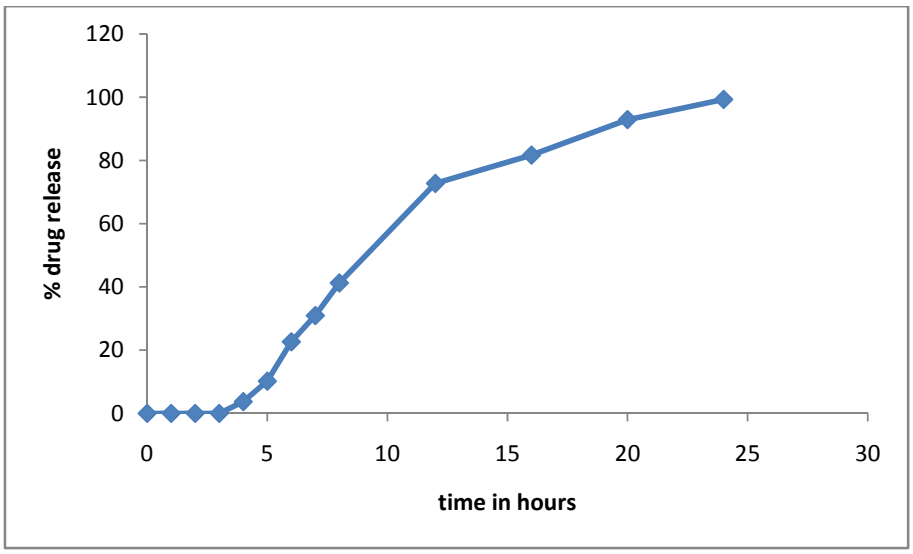


Fig.15 in vitro drug release profile of carvedilol F7(EC:PVP 1:1)

Table 24: Dissolution profile of formulation F8* containing carvedilol using buffer pH 1.2 and 6.8

Time (hr)	Absorbance (290 nm)	Amount (µg/ml)	Amount (mg/900ml)	Cumulative %release
1	0	0	0	0
2	0	0	0	0
3	0	0	0	0
4	0.032	1.31	1.18	4.72
5	0.058	2.40	2.16	8.68
6	0.164	6.72	6.04	24.27
7	0.224	9.18	8.26	33.25
8	0.277	11.36	10.22	41.29
12	0.489	20.04	18.19	72.76
16	0.567	23.23	20.91	84.67
20	0.601	24.63	22.16	90.15
24	0.652	26.72	24.04	98.17

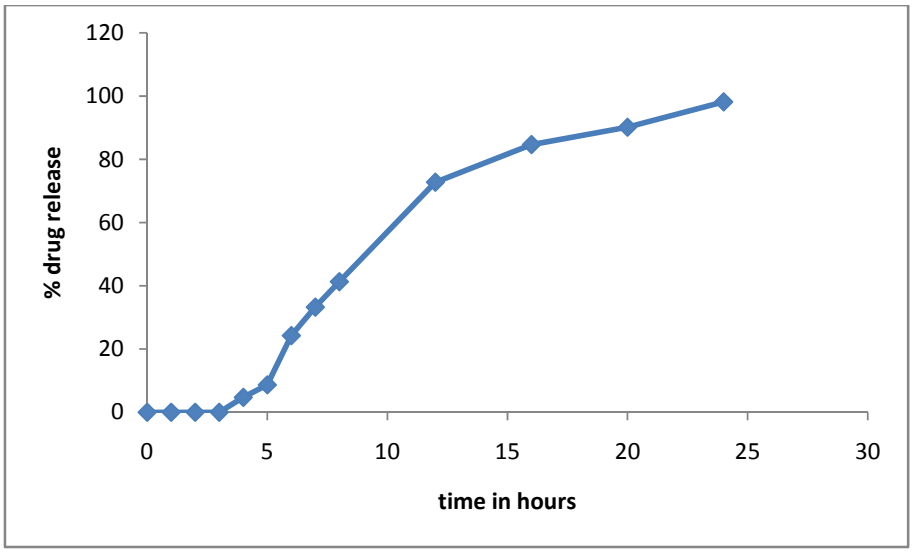


Fig.16 in vitro drug release profile of carvedilol F8 (EC:PVP1:1)

Table 25: Dissolution profile of formulation F9* containing carvedilol using buffer pH 1.2 and 6.8

Time (hr)	Absorbance (290 nm)	Amount (µg/ml)	Amount (mg/900ml)	Time (hr)
1	0	0	0	0
2	0	0	0	0
3	0	0	0	0
4	0.023	0.94	0.85	3.40
5	0.047	1.5	1.76	7.07
6	0.127	5.22	4.70	18.86
7	0.178	7.32	6.59	26.54
8	0.288	9.34	8.40	33.94
12	0.423	17.33	15.60	62.94
16	0.511	20.94	18.84	76.23
20	0.567	23.23	20.91	84.91
24	0.643	26.35	23.71	96.59

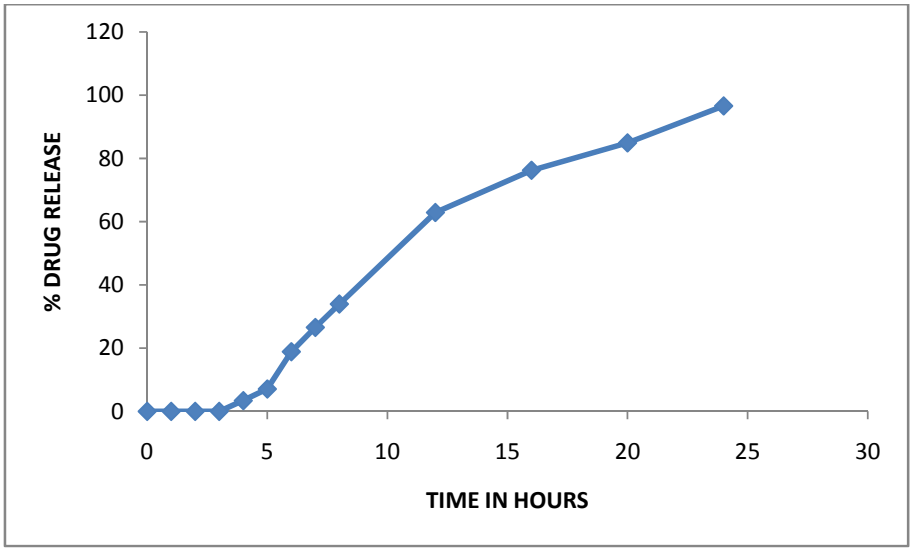


Fig. 17 in vitro drug release profile of carvedilol F9 (EC:PVP1:1)

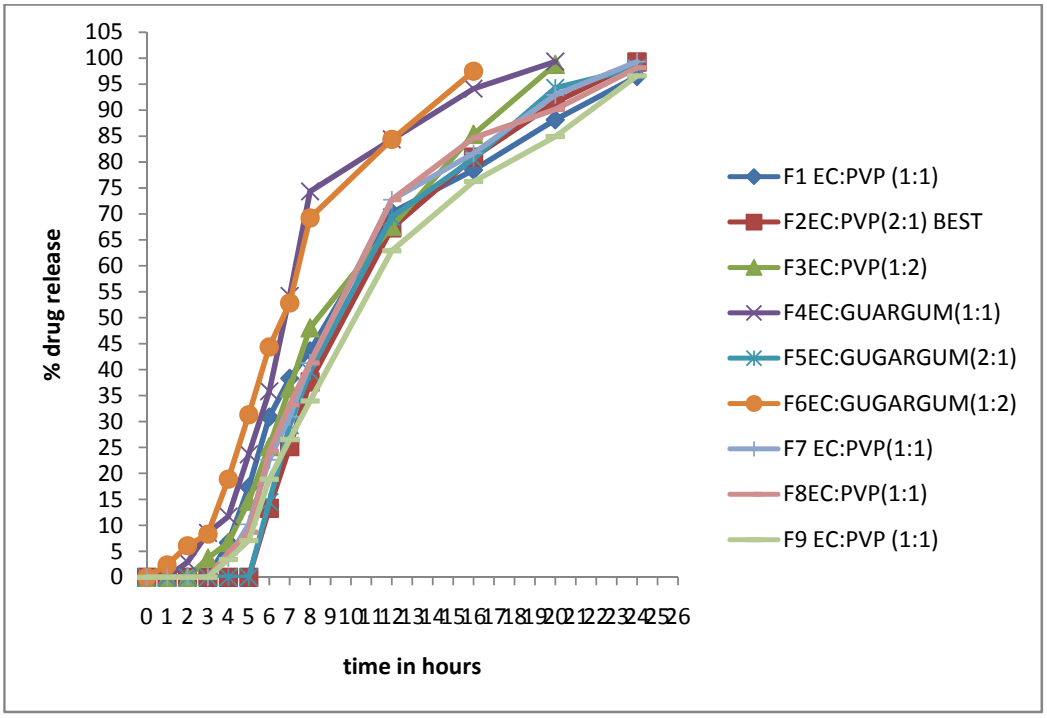


Fig.18 in vitro drug release profile of carvedilol F1-F9 coated with PVP/EC/guar gum

Kinetic Analysis of *in-vitro* Release Rates of Compression Coated Carvedilol Tablet: [26]

In order to define the transport mechanisms and type of release, four kinetic models where applied the zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration. The first order Eq. (2) describes the release from system where release rate is concentration dependent. Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). Korsmeyer derived a simple relationship which described drug release from a polymeric system Eq. (4). To find out the mechanism of drug release, drug release data was fitted in Korsmeyer–Peppas model

The result of in vitro release profile obtained for optimized formulations F2 were plotted in mode of data treatment as follows: -

1. Zero - order kinetic model: This follows, Cumulative % drug released Vs time.
2. First – order kinetic model: This follows, Log cumulative percent drug remaining Vs time.
3. Higuchi's model: This follows, Cumulative percent drug released Vs square root of time.
4. Korsmeyer equation / Peppa's model: This follows, Log cumulative percent drug released Vs log time.

Zero order kinetics:

Zero order release would be predicted by the following equation: -

$$A_t = A_0 - K_0 t$$

Where,

A_t Is Drug release at time't'.

A_0 = Initial drug concentration.

K_0 = Zero - order rate constant (hr^{-1}).

When the data is plotted as cumulative percent drug release Vs time, if the plot is linear then the data obeys Zero – order kinetics and its slope is equal to Zero order release constant K_0.

First Order Kinetics:

First – order release would be predicted by the following equation: -

$$\text{Log } C = \log C_0 - Kt / 2.303$$

Where,

C = Amount of drug remained at time't'.

C_0 = Initial amount of drug.

K = First – order rate constant (hr^{-1}).

When the data plotted as log percent drug remaining Vs time, yields a straight line, this indicates that the release follows first order kinetics. The constant 'K_1' can be obtained by multiplying 2.303 with the slope value.

Higuchi's model:

Drug release from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation: -

$$Q = [D\varepsilon / \tau (2 A - \varepsilon Cs) Cst]^{½}$$

Where,

Q = Amount of drug released at time't'.

D = Diffusion coefficient of the drug in the matrix.

A = Total amount of drug in unit volume of matrix.

Cs = the solubility of the drug in the matrix.

ε = Porosity of the matrix.

τ = Tortuosity.

t = Time (hrs) at which 'q' amount of drug is released.

Above equation may be simplified if one assumes that 'D', 'Cs' and 'A' are constant. Then equation becomes: -

$$Q = Kt^{1/2}$$

When the data is plotted according to equation i.e. cumulative drug release Vs square root of time yields a straight line, this indicates that the drug was released by diffusion mechanism. The slope is equal to 'K' (Higuchi's 1963).

Korsmeyer equation / Peppa's model:

To study the mechanism of drug release from the sustained-release matrix tablets of Diltiazem Hydrochloride, the release data was fitted to a well-known exponential equation (Korsmeyer equation/ peppa's law equation), which is often used to describe the drug release behavior from polymeric systems.

$$M_t / M_\alpha = Kt^n$$

Where,

M_t / M_α = The fraction of drug released at time't'.

K = Constant incorporating the structural and geometrical characteristics of the drug / polymer system.

n = Diffusion exponent related to the mechanism of the release.

Above equation can be simplified by applying log on both sides,

And we get: -

$$\text{Log } M_t / M_\alpha = \text{Log K} + n \text{ Log t}$$

Table 26: Mechanism of drug release as per korsmeyer equation / peppa's model.

S. No.	n Value	Drug release
1.	< 0.45	Fickian release
2.	0.45 <1.0	Non – Fickian release
3.	> 1.0	Class II transport

When the data is plotted as log of % cumulative drug released Vs log time, it yields a straight line with a slope equal to 'n'. For Fickian release 'n' = 0.45 while for anomalous (non - Fickian) transport 'n' ranges between 0.45 and 1.0.

Table 27: Drug release kinetics study of optimize batch F2

Time (hr)	%drug release	% drug remaining	Log % drug remaining	logt	Square root of t	Log % drug release
1	0	100	2	0	1	-
2	0	100	2	0.3010	1.4142	-
3	0	100	2	0.4771	1.7320	-
4	0	100	2	0.6020	2	-
5	0	100	2	0.6989	2.2360	-
6	13.27	86.72	1.9381	0.7781	2.4494	1.123
7	25.15	74.84	1.8742	0.8450	2.6457	1400
8	37.62	62.37	1.7950	0.9030	2.8284	1.575
12	67.28	32.71	1.5147	1.0791	3.4641	1.827
16	80.93	19.06	1.2802	1.2041	4	1.908
20	91.53	8.46	0.9277	1.3010	4.4721	1.961
24	99.3	0.70	-0.1331	1.38021	4.8989	1.996

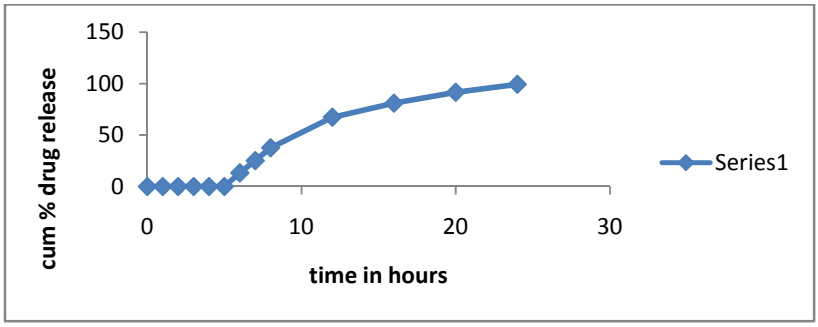


Fig. 19 Shows zero order kinetics of F2

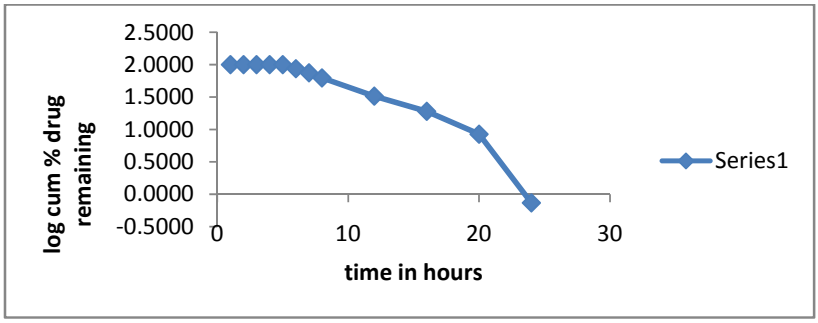


Fig.20 Shows first order kinetics of F2

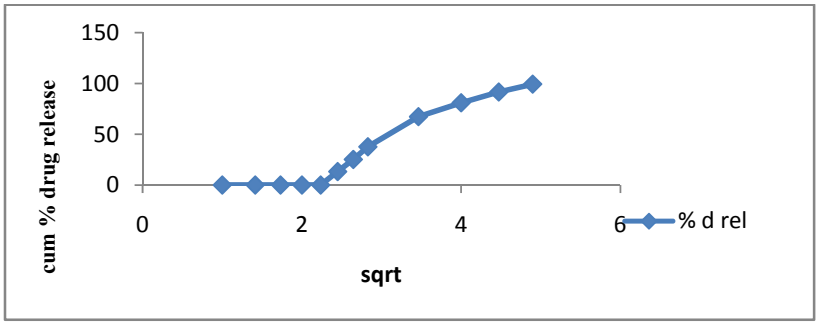


Fig. 21 Shows higuchi model for F2

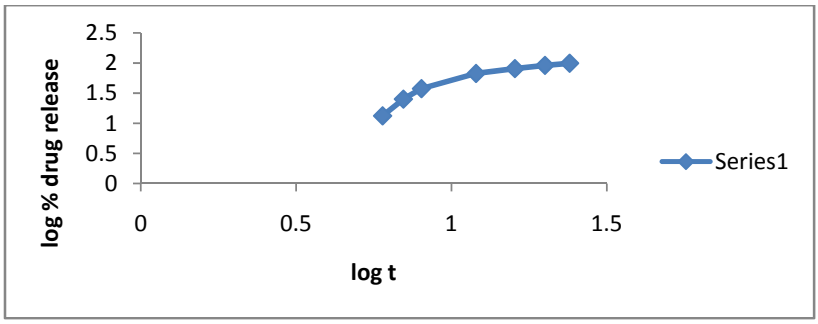


Fig. 22 Shows peppa's model for F2

Table 28: Result of model fitting of batch F2

Formulation	Zero Order R^2	First Order R^2	Higuchi model R^2	Korsmeyer's Plot R^2
F2	0.9392	0.8826	0.9252	0.8878
				n=1.322

Transverse and longitudinal section view of press coated tablets[33]

Tablets were cut transversely and longitudinally by using blade individually. The cutting sections of tablets were evaluated by digital camera.

Fig.23 shows the external appearance of the press coated tablets of formulation

Transverse section view

Longitudinal section view

Fig .24 Transverse and longitudinal section view of press coated tablets.

Stability Studies of the Optimized Formulation[35]

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions, re-test periods and shelf-lives to be established.

ICH specifies the length of study and storage conditions:

Long term testing: $25^0C \pm 2^0C$ /60% RH ± 5% RH for 12 months.

Method

Accelerated testing: $40^0C \pm 2^0C$ /75% RH ± 5% RH for 6 months.

In the present study, stability studies were carried out at $40^0C \pm 2^0C$ for a time period of 90 days for selected optimized formulations.

For stability study, the tablets were placed in amber colored vials and sealed with aluminum foil. These sample containers were placed in desiccators.

Evaluation of samples: The samples were analyzed for the following parameter,

Physical evaluation:

Appearance: The samples were checked for any change in color at every week.

Hardness: The samples were tested for hardness at every week.

Chemical evaluation:

Drug content: The samples were checked for drug content.

Drug release: The samples were subjected to drug release studies.

Table 29: *in vitro drug* release study of F2 optimized bacth

Time in hours	F2 Zero month	F2 1st month	F2 2nd month	F2 3erd month
1	0	0	0	0
2	0	0	0	0
3	0	0	0	0
4	0	0	0	0
5	0	0	0	0
6	13.27	13.52	13.75	13.89
7	25.15	25.61	26.12	26.12
8	37.62	37.62	37.89	37.91
12	67.28	67.43	67.64	67.71
16	80.93	81.0	81.2	81.25
20	91.53	91.72	91.98	92.1
24	99.3	99.1	98.9	98.7

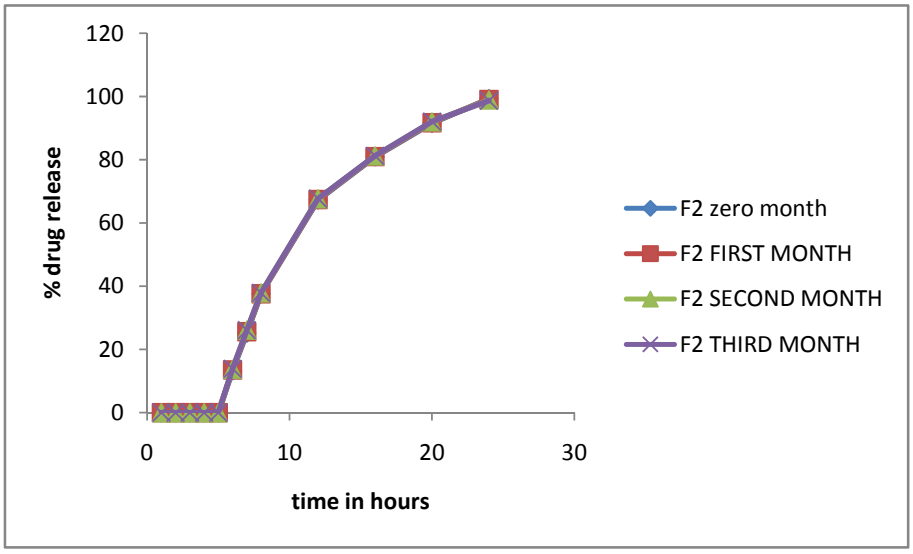


Fig. 25 in vitro drug release study of F2 optimized batch

Table 30: Different Parameters of stability study

Paramater	At temp$40^0 \pm 2^0$c RH 75%±5%			
	F2 zero month	**F2 1st month**	**F2 2nd month**	**F2 3ed month**
apprance	Off white	Off white	Off white	Off white
Weight(mg)	152	No change	No change	No change
Thickness(mm)	3.30	No change	No change	No change
Hardness(kg/cm^2)	5.2	No change	No change	No change
% drug content	99.33	99.03	98.79	98.23
% drug release	99.3	99.1	98.9	98.7

DISCUSSION

The aim of this work was to develop a chronotherapeutic delivery of carvedilol in the form of press coated tablets. In this study we develop a chronological dosage form to release the drug in the early morning between 3a.m to 6a.m because rennin, cortisol, angiotensin, aldosterone were secreted in peak level, most of the cardiovascular disorders such as angina pectoris, sudden cardiac death, stroke occurs in this time, the designed formulation was planned to taken at bedtime and the focus was to optimally deliver the drug in higher amounts in the early morning hours and lower amount at night.

The prepared press coated tablets (F1 to F9) were used for evaluation of compatibility studies, physico-chemical parameters such as hardness, friability, thickness, weight variation, drug content uniformity, *in vitro* release and *in vitro* release kinetics.

PREPARATION OF STANDARD CURVE OF CARVEDILOL:

From the standard curve of Carvedilol it was observed that the drug obeys beer's law in concentration range of 1-5 µg/ml in acid buffer (pH 1.2) and phosphate buffer (pH6.8).

COMPATIBILITY STUDIES

The compatibility studies between the drugs and excipient were evaluated by using IR matching approach. The IR spectrum of excipient with drug was compared with the standard spectrum of carvedilol. In carvedilol IR spectrum, principal peaks were noticed at following wave numbers 3344.68, 1305.24,3058.24, 2923.22, 1696.76, 752.26,2923.22 cm^{-1} (KBr pellet). There was no appearance or disappearance of characteristics peaks. The IR spectra obtained are given in fig 6,7 and 8. This method confirms the absence of any chemical interaction between drug and excipient.

Formulation:

Nine different press coated tablets of carvedilol were formulated by using various proportions of different polymers such as HPMC, ethyl cellulose, polyvinylpyrrolidone and guar gum by direct compression method. All the formulations were prepared by keeping constant tablet weight (150mg ± 15mg) and hardness (5.2 ± 0.5 kg/cm^2).

EVALUATION PARAMETERS:

Physicochemical Evaluation:

The blend powder of all the batches exhibited good flow characteristics evident from the results of their physicochemical evaluations. The angle of repose value ranged from 23.14" to 26.26" for core and 23^{0}14" to 26^{0}38"for coating material. The results were found to be below 28^0 and hence the blend showed to have good flow ability. Bulk and tapped densities are used for the measurement of Compressibility index. The Bulk density ranged from 0.057to 0.660 for core and 0.689 to 0.769 for coating material.

While tapped density ranged from 0.578 to 0.721for core and 0.769 to 0.869 for coating material. The compressibility index (%) was calculated from the Bulk density and it ranged from 11.41 to 19.51 for core and 10.344 to 14.814 for coating material. The blend was found to have free flowing property as the result were found to be below 20%. The Haussner's ratio ranged from 1.03 to 1.18 for core and 1.116 to 1.174 for coating material. The result indicates the free flowing properties of the powder as the value was below 1.2. (table 7 & 8)

The prepared tablets were subjected to evaluation tests such as hardness, thickness, % weight variation, friability and drug content. All the nine formulations had shown results for these characteristics within the acceptable ranges.(table 13,14 & 15)

***IN VITRO* DRUG RELEASE PROFILE:**

From the results of *in vitro* studies all the prepared press-coated tablets (F1 to F9) were given a good release in the range of 96.5% w/v to 99.3% w/v. The formulation F2 [25mg of carvedilol, EC: PVP (2:1)] and F5 [25mg of carvedilol, EC: Guar gum (2:1)] were shown ideal release for chronotherpeutics. Because of

having a lag time of 5 hours and maximum release of 99.3 % w/v and 98.1 % w/v respectively. The *in vitro* dissolution data are given in Table 18 and 21 and fig. 10 and 13 respectively.

The profiles clearly indicate that the carvedilol released from the press coated tablet exhibited a unique release profile depending on the amount of PVP and EC used and also HPMC polymer in core tablet contributes in drug release for prolonged period. The profile exhibited a lag time (induction period) followed by a prolonged drug release throughout a day. The drug was released from the press-coated tablet after a lag period of 5-6 hours, depending upon the weight ratios of EC and PVP. The swelling of the outer shell of press-coated tablets is a key factor to achieve the time-controlled delivery. The drug was released from the core tablet after rupturing, caused by the pressure build up with in the core system. Increasing the concentration of EC in the formulation of the outer shell, the lag time was increased. The lag time changed according to weight ratios of the EC and PVP as follows. F3 < F1 < F2

The dissolution profile of EC/guar gum was also similar to that of the dissolution profile of EC/PVP, showing a distinctive inducting lag followed by drug release. The lag time of the press coated tablets containing (1:1, 2:1, 1:2) ratios of EC/guar gum was F6 < F4 < F5 respectively.

It is evident that the time lag of press coated tablet changes by varying the amount of EC and PVP and guar gum in the outer shell. The dissolution profile of F7 & F8 formulation shows that the release rate is independent of the drug concentration. Increase in amount of HPMC in core tablet (formulation F9) increases the lag time. The dissolution profile of all the formulated carvedilol time controlled release tablets were reported in Table 16.

CURVE FITTING DATA ANALYSIS:

The *in vitro* drug dissolution result of batch F2 was used for in various mathematical models (zero, first, Higuchi's square root and Pappas equation) to evaluate the kinetics and mechanism of drug release from the tablets. The model that best fits the release data is selected based on the correlation coefficient (r) value in various models. The model that gives high 'r' value is considered as the

best fit of the release data. The release constant was calculated from the slope of the appropriate plots, and the regression coefficient (r^2) was determined (Table 28). It was found that the in vitro drug release of optimize batch F2 was best explained by zero order model as the plots showed the highest linearity (r^2 = 0. 9392), Followed by Higuchi's model (r^2 = 0.9252),Korsmeyer–Peppas model (r^2 = 0.8878), and first order (r^2 = 0.8826). Drug release was also found to be close to zero-order kinetics, indicating that the concentration was nearly independent of drug release. The corresponding plot (log cumulative percent drug release vs. log time) for the Korsmeyer - Peppas equation indicated a good linearity (r^2 = 0.8878). The release exponent n was 1.32, which appears to indicate drug release rate was independent of time and controlled by a swelling mechanism (case II transport) it mean that follows Zero order drug release mechanism. Drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred to as square root kinetics (or Higuchi's kinetics). Kinetic models which fit zero order and Higuchi are more suitable for controlled release formulations.

Transverse and longitudinal section view of press coated tablets

Transverse and longitudinal sections of press coated tablets were made using surgical blade in order to verify the position of position of core tablet. Fig.24, shows the photographs of these sections. From this, it is clear that core tablet is placed in centre of coated tablet.

STABILITY STUDIES:

The stability study of the optimized batches in which the tablets were monitored up to 3 month at accelerated stability conditions of temperature and relative humidity ($40^0 \pm 2^0$C, RH 75% ± 5%) (Table No 29). There was little bit but no large difference was observed in the evaluation of the optimized batch. The dissolution study of the optimized batch at zero month and third month show some changes in drug release profile. (Fig. 25) Both the dissolution study show the typical pulsatile profile but drug release was somewhat decreas.

SUMMARY AND CONCLUSION

The main focus of chronotherapeutic formulation of carvedilol is to optimally deliver the drug in higher amounts in early morning hours (i.e. at time of greatest need) and lower amounts at night (i.e. when the need of drug is less). Because systolic blood pressure and diastolic blood pressure rapidly rise in the early morning by at least 15 to 25 mm Hg and reach highest levels late in the day. Typically SBP and DBP decline in sleep by 10% to 20% from daytime.

From the results it was concluded formulation **F2** (EC:PVP, 2:1) and **F5** (EC:guar gum, 2:1) shows lag time of 5 hours consistent with requirement for **chronotherapeutics** and the drug release was extended as shown in fig.11 and 14. The best lag time could be achieved by higher the concentration of EC in outer shell. The lag time could also be controlled by altering the weight ratios and viscosity grade of polymers. Hence control onset extended press coated carvedilol tablets can provide a useful means for timed release and may be helpful for BP patients with morning surge, which results in better compliance by patients and fewer side effects.

In **conclusion**, the time lag of press-coated tablet could be modulated by choosing the type and amount of excipient used in the outer shell to achieve the time controlled disintegration according to the time required The present study indicated that the lag time of the press-coated tablet can be suitably modulated by formulating the outer shell with ethyl cellulose and PVP or guar gum.

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